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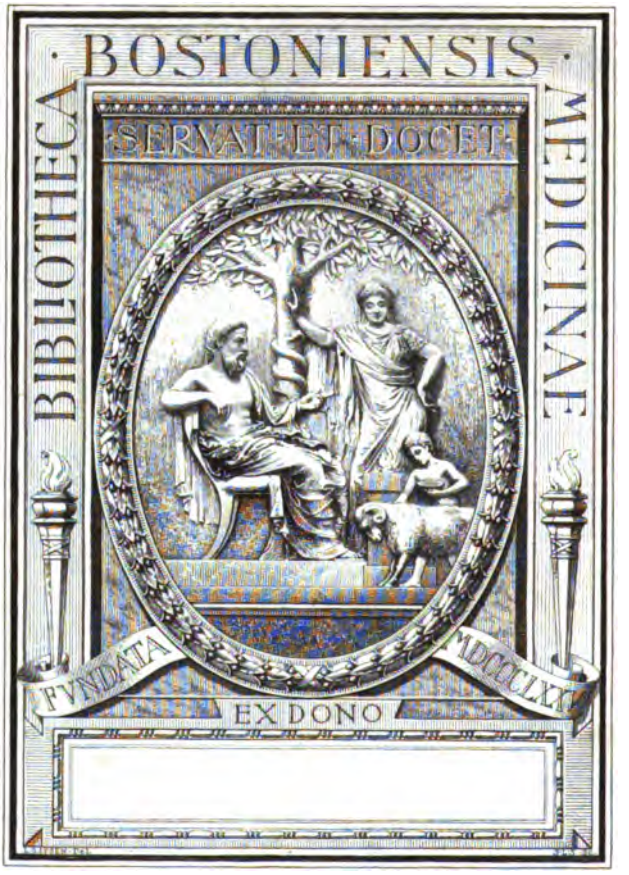
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Reports

FROM THE

CANCER RESEARCH LABORATORIES.

VOLUME I.

VOLUME I.

Reports from the Cancer Research Laboratories: The Middlesex Hospital.

EDITED FOR THE CANCER INVESTIGATION COMMITTEE

BY

ALEXANDER G. R. FOULERTON, F.R.C.S.,

DIRECTOR OF THE CANCER RESEARCH LABORATORIES;
MEMBER OF THE COMITÉ FÜR KREBSFORSCHUNG.

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EDITORIAL NOTE.

THE original intention with regard to the issue of Reports from the Cancer Research Laboratories was that one Volume should be issued in connection with the completion of each series of five hundred cases of malignant disease investigated in the Laboratories.

The first series of five hundred cases was completed in the earlier part of this year, but it was found that it would be convenient to issue the first Volume of Reports before the material from this series of cases had been completely worked up. And the second Volume of these Reports, which it is hoped will be published early next year, will include a detailed account of these five hundred cases, together with any further results of research work.

The present Volume includes an Introduction, for which we are indebted to the kindness of Dr. SIDNEY COUPLAND, Consulting Physician to The Middlesex Hospital, and original Papers by two voluntary workers in the Laboratories, Dr. HENRY W. P. YOUNG and Mr. C. PRICE-JONES, M.B., which were completed in July of last year and April of the present year respectively.

My best thanks are due to Mr. HILLIER for much assistance which he has given in the preparation of the present Volume of Reports.

ALEXANDER G. R. FOULERTON.

THE MIDDLESEX HOSPITAL, LONDON.
August, 1902.

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REPORTS

FROM THE

CANCER RESEARCH LABORATORIES.

INTRODUCTION.

THE CANCER CHARITY OF THE MIDDLESEX HOSPITAL, 1792—1902.

By SIDNEY COUPLAND, M.D., F.R.C.P.,
CONSULTING PHYSICIAN TO THE MIDDLESEX HOSPITAL.

On the 19th of June 1792 a ward was opened at The Middlesex Hospital for the reception of patients suffering from cancer, in accordance with resolutions passed at a special Court of Governors on the 19th January—"1. That a ward, capable of holding ten or twelve beds, shall be immediately fitted up and furnished. 2. That when the ward is completely fitted up and furnished patients shall be admitted, and that at least six, if so many shall offer, shall be there constantly maintained." There were other resolutions bearing on the same subject, one of which provided that such patients should remain an unlimited time, "until either relieved by art or released by death, unless it should be thought necessary to discharge them for ill-behaviour." It also provided for an out-patient department, where persons afflicted with cancer could obtain advice and medicine. The seventh resolution ran: "That in conformity to the particular wish of the benevolent donor, the name of every patient admitted into the ward fitted up for the reception of patients afflicted with cancer shall be entered in a journal; and when, in the judgment of the medical gentlemen of the

Hospital, any extraordinary circumstance may occur, or any remedy be discovered, a record shall be made and kept of the same for the inspection of the public, agreeably to the spirit of the original paper presented by Mr. Howard, which the donor particularly requests may be strictly adhered to."

From that day to this—a period of 110 years—the Cancer Department of The Middlesex Hospital has remained a distinctive feature of the establishment, having its separate foundation, and affording a refuge to a vast number of unfortunate persons who have been the subjects of an insidious and incurable disease. The department, from the benefactions received from time to time, has been considerably extended since the single ward was opened, but throughout the whole course of its history it has been conducted in the spirit of its founder, of which the investigations recorded in the present volume are the latest exemplification. A brief sketch of the origin and aims of this Charity, in some respects unique, may, it is thought, fittingly introduce this volume.

The first step was taken in a letter addressed to "The medical gentlemen of The Middlesex Hospital" by Mr. John Howard, surgeon, of Argyll Street, on 12 October 1791. It ran as follows:—

"Gentlemen,

"The deplorable situation of paupers afflicted with the disease called a cancer was casually a topic of conversation, and, in consequence of that conversation, I was requested to put down in writing what I conceived were the best means of affording relief to such persons by a public institution.

"The present state of The Middlesex Hospital—the funds of which are small when compared with some others—its want of immediate patronage, and having at this time several wards unoccupied, were the circumstances which occasioned the present application.

"To professional men it becomes me to write with diffidence, and any amendment of the plan I shall presently mention will be received with pleasure.

"I take the liberty to observe that two principal objects present themselves to my mind on this occasion, namely, the relief of persons suffering under this disease, and the investigation of a complaint which, although extremely common, is, both with regard to its natural history and cure, but imperfectly known.

"For the attainment of the first object, it is proposed that an airy ward of The Middlesex Hospital be appropriated to this specific disease, and to this disease only; that the diseased shall there find such an alleviation of their sufferings as their respective situations may require, and that for an unlimited time.

"That one large airy ward divided into two, one part for men and the other for women, or two distinct wards, containing ten or twelve beds, might be fitted up if a sufficient fund could be raised; and the ward or wards being already built, there would be wanting only the usual furniture of beds, coal, candles, board, and nursing; and, I believe, the expense of the above articles, including medicines, may amount to about £20 *per annum* for each of the ten or twelve; and, as some patients would go off as others come in, within the space of a year there may probably be about forty in-patients relieved in succession.

"The worst and most deplorable cases of cancer may be divided into two classes—in the one class the symptoms proceed to their final termination rapidly, in the other slowly.

"The first of these classes, as it will contain the more distressing and speedily-destructive cases, will comprehend the most proper objects for admission as in-patients. Among these will be reckoned scirrhus and cancerous tumours, proceeding with such quickness in their progress that they readily admit of a removal at an early, but not at a distant period; and also spreading ulcerated cancers, both when relievable by art and when not.

"The second class will comprehend such women as have cancers not admitting of any operation, the disease going on slowly in its own natural course for years. These cancers, although generally adherent, are frequently not ulcerated, nor do they, when so circumstanced, greatly impede the ordinary business of life. Such cases, however, are not only objects of charity, but curious subjects for investigation, and therefore may be relieved as out-patients, with the liberty of being admitted within the Hospital whenever their symptoms should become more distressing or require constant daily attendance.

"And, that an opportunity may not be wanting of improving our knowledge of the disease and present methods of cure, I beg leave to suggest farther, that, whenever the fund of the institution shall enable the Governors to do so, a power be then given to the medical gentlemen of the Hospital to admit occasionally, either as in- or out-patients, such cases of scrofula or leprosy as may lead to the knowledge of cancer or be liable to become cancerous; and that they may be at liberty to recommend, when necessary, warm or cold sea-bathing at the sea, mineral waters, or country air, for such cases as may require more particularly these remedies in aid to other means of relief.

"With regard to the second object, namely, the investigation of the disease, Lord Bacon has observed that medical men should make themselves proficients in physic by studying one disease at a time. It is an opinion worthy of so great a man; it was particularly adopted by the late Mr. Pott, and by him recommended to all students in surgery.

"By confining one or more wards to cancer only, the attention of pupils and others will be directed very strictly to the study of this disease. They will see facts as they arise in the aggregate from a large number of patients; new lights will appear, and new discoveries will probably be made.

"'I have often thought,' says Dr. Sydenham, 'that if I knew accurately the natural history of any disease, I should never be at a loss for a proper method of treating it;' and the wonderful improvements he made in science by his great attention to the natural history of diseases, and the effects of medicine upon them, have been justly admired by practitioners of every country. (*Vide* the Preface to Dr. Sydenham's "Observations on the History and Cure of Acute Diseases.")

"The natural history of cancers, although a common disease in the enlarged comprehensive sense in which this great man understood the natural history of diseases, is but little known. I would therefore, in order to improve a subject on which a successful practice greatly depends, propose that a faithful account of the history and circumstances of every case be kept: its antecedents and consequences should be marked, the effects of medicine and of operations, when necessary, noted, together with all the collateral helps to be gained by an inquiry into constitutional habits and diseases not strictly cancerous, but probably connected with it. This examination may be made by a medical gentleman of the hospital with the patient before him, his notes to be corrected by himself, and kept as a record of the history and circumstances of each case, to be recurred to, as an authority, by any intelligent or scientific person. A copy of these notes may be kept, fairly written, for general inspection; and if anything extraordinary or worthy of more particular notice arise from these sources, let the circumstances be published to the world at large.

"By an institution comprehending the two objects now pointed out, I have a hope not only that the diseased, but that practitioners in general may be benefited, that much useful knowledge may be disseminated, and that we may, in no great length of time, be furnished with documents on the disease and cure much more authentic than any we are at this time in possession of. It is a very important subject of inquiry, equally interesting to the rich and independent part of mankind as to the poor; and if such an institution be fairly set on

foot, it cannot fail of producing beneficial consequences to all descriptions of persons labouring under this dreadful malady.

"Having now, gentlemen, submitted to your consideration ideas which have arisen in the way above mentioned, I leave their completion with you to be amended by such further additions as may arise from the action of minds embarked in the same cause—that of useful science.

"I will only add (and I repeat their names with reverence) that a better instructor in all philosophy is not to be found than Lord Bacon; and that after the lapse of more than a century, regard being had to subsequent improvements, there is not a brighter example of sound, unsophisticated physic than Dr. Sydenham; nor, I believe, a better guide to surgery than the late Mr. Pott.

"I am, with the greatest respect,
"Gentlemen,
"Your most obedient servant,
"JOHN HOWARD.

"Argyll Street,
"October 12, 1791."

The letter was favourably received, and with praiseworthy promptitude the Board of the Hospital invited the attendance of Mr. Howard, who laid before it the proposals of his anonymous friend in furtherance of the object they had in view, which had arisen out of the "casual conversation" mentioned in the letter. The proposal at first was to contribute £3000 for the endowment of a cancer ward, and an additional £400 to fit it up, this being subsequently modified by the donor to a proposal to place "as much money in the 3 per cent. Consols, in the names of William Drake, jun., Esq., Mr. John Howard of Argyll Street, and the Treasurers of the Hospital for the time being, as trustees, as should furnish an annual income of £120, and also that he would pay the expense of fitting up and furnishing the ward for the reception of ten or twelve cancerous patients." The proposal and plan were accompanied by an Explanatory Paper by Mr. Howard, who subsequently republished all the documents relative to this foundation, together with "Notes and Observations,"* which fairly well illustrate the state of knowledge of

* "The Plan adopted by the Governors of The Middlesex Hospital for the Relief of Persons afflicted with Cancer: with Notes and Observations." By John Howard, surgeon. (London, 1792. 12mo.)

cancer at this time, and also the scientific spirit which animated the desire to found this special sphere of observation. From the Explanatory Paper, addressed to the Court of Governors, it may suffice to quote a few paragraphs, which again shew what was in the mind of the founder and his surgical friend in making the proposal :—

"The fund proposed for this institution, liberal as it undoubtedly is, does not preclude the receipt of other subscriptions. The intention of the donor is only to make a handsome beginning, in the hope of many contributions from the charitably-disposed to the farther extension of the plan.

"It is wished that relief may be given, in every stage of the disease, to a large number of patients afflicted with cancer, and that the accession of medical knowledge hereby arising may be generally and widely diffused.

"It is presumed such an institution, although supported by a separate subscription, will tend to the aggrandisement of The Middlesex Hospital, for in no particular is the subsisting economy deranged; that economy is strengthened and enlarged by the addition of new resources, backed by immediate patronage, which may probably be the means of raising future subscriptions to a great amount. The business of the house will continue to go on in the usual way. It is no impediment to so benevolent a foundation; it only enlarges the sphere of action by holding out relief to poor cancerous patients (many of whom are not now received into any hospital, or, if received, are soon discharged without finding benefit), and by attempting to investigate scientifically the nature and cure of a disease which, from the character of incurable hitherto annexed, has been long, much too long, neglected."

He then describes the class of cases it is intended to relieve, distinguishing those which are from those which are not suitable for operation, and those that can be treated as out-patients, and goes on to say :—

"From the foregoing outline it is clear that the plan embraces not only the most distressing objects, but every symptom and circumstance of the disease; abstracted therefore from the relief and comfort it will afford to many a suffering individual, there will be a fair scope for investigation and improvement, which no institution upon a smaller scale could possibly give.

"Had the affair of investigation been omitted, the plan would not only have been extremely imperfect, but it would neither have filled the mind nor have answered the intentions of the donor. I can only

say he has the whole matter much at heart. He does not mean to prescribe to the medical gentlemen of the house, but hopes that this part of the plan will be kept up with due attention and spirit . . . ."

The "Notes and Observations," which Mr. Howard appends to the reprint of his letter, occupy some fifty of the eighty pages of the duodecimo pamphlet. They are very interesting as being mainly composed of records of his personal experiences in the treatment of cancerous affections, but space does not permit any quotation of them here. At the same time it would hardly be fair to him, who must be considered as the prime originator of the idea so happily carried into effect through his friend's generosity, to omit the following passages with which he closes this little treatise:—

"When the reader reflects that one great object of the proposed institution is to preserve from oblivion the circumstances of such cases as may occur; when he foresees that these will probably be numerous, and that the record will be carefully kept and its contents freely communicated, he may form some idea of the utility of this part of the plan, and of the immense advantage it will be, not only to medicine, but to mankind in general.

"Having had the honour of bringing forward a difficult public business in a regular scientific way, I beg leave in vindication of the ready adoption the plan has met with from the Governors and medical gentlemen of The Middlesex Hospital, and to shield both them and myself from every idea of quackery, to observe that their attention and cares will be considerably increased without an adequate compensation. And, as to myself, I derive no advantages from the institution. I have only the pleasure of having aided confidentially, and to the best of my judgment, the good intentions of my friend.

"The medical gentlemen of the house are in full possession of the sentiments of the donor, and, being men of known character, there cannot be a doubt but the business will be conducted in a proper manner. Their conduct will be a lesson to those who are to come after them and an example to all mankind, shewing, on the firm Hippocratic ground, with the assistance of the experimental knowledge of the present day, how much may be done practically towards the advancement of this part of medicine by industry, a well-directed arrangement, and a fortunate combination of circumstances."

The name of the unknown benefactor was not revealed until after his death in 1796. Mr. Howard, in apprising the Hospital

authorities of this event, says that it was Mr. Samuel Whitbread who had made the gift, and mentions further that it was "the wish of that great and good man, expressed to me some months before his death, that the present Samuel Whitbread, Esq.,* might be appointed one of the trustees in place of the late Mr. Drake, a nomination which will meet I hope with the full approbation of the Board and Governors at large, and which I have authority to say will be accepted . . . ."

In the following year Mr. Howard was requested by the Court of Governors to accept the appointment of surgeon-extraordinary to the cancer establishment, an office which he held until his death in 1811. Of John Howard himself we know little. It is clear that he was a cultured and well-read man, with liberal and enlightened views, and imbued with the true scientific spirit. This much appears from the scanty writings he has left behind him, and even in the passages above quoted it is not difficult to discern these characteristics. He must also have been a man of humanitarian disposition—and it is noteworthy that Samuel Whitbread was also the close friend

* Samuel Whitbread the younger was M.P. for Bedford, and an active Whig politician. He took great interest in the cancer establishment, and only a month before his tragic end—he committed suicide on 6 July 1815—he had written a preface to a work by Mr. Young on the treatment of cancer by compression, in which he urged the claims of the method on the attention of the Governors of the Hospital. We shall have occasion to refer to this book later. Mr. Whitbread took a very active part in securing the election of Charles Bell as Surgeon to The Middlesex Hospital. Bell heard of his death when weatherbound at Ostend on returning from a visit to the field of Waterloo, and notes in his diary: "We hear much of the Allies in Paris, of the Armistice, and of Whitbread. Alas! how sincerely I lament him. He did much for me in a matter I had much at heart. He seemed to have a hearty, kindly manner to me quite at variance with his public character. He seemed a man made to buffet with the world—to kill himself! I am yet inclined to say it is a lie. It is this more than the state of unpleasant suspense in which I am kept that frets me with the time. How precious is a just way of thinking, a love for mankind, a desire for doing good, which I think was likely to prevent a man from letting this gloom overshadow him and obscure his reason; besides, is there not a terrible disregard for the feelings of others in this act?" ("Letters of Sir Charles Bell," 1870, p. 239). On the same subject Crabb Robinson writes in his diary, 7 July: "I called on Amyot early, and found on going out that Paris had been again taken by the Allies. But the public did not rejoice, for Paris had capitulated on honourable terms, and Buonaparte had escaped. During the day Mr. Whitbread's death was more a subject of interest than the possession of Paris. The death of so watchful a Member of Parliament is really a national loss. He belonged to the noblest class of mankind" ("Diary, Reminiscences, and Correspondence," third edition, 1872, vol. i., p. 258).

of the other John Howard, the philanthropist (1726—1790), a fact which, taken together with the qualities disclosed by their individual acts, makes one think it possible that the two Howards were kinsmen; at any rate, if not allied by ties of blood, they were akin in the noble desire to benefit their fellows, and in this they had the practical sympathy of their mutual friend.

The name of "Whitbread" was given to the Cancer Ward in 1815, the Governors doubtless intending to commemorate thereby both the founder and his son, who for twenty years had been a zealous friend of the Hospital, and especially of the cancer charity. About this time also an opportunity for increasing the number of beds on the foundation accrued by the bequest of £5000 Consols by Dame Alithea Maria Stafford, and it was then, I believe, that male patients were received on the foundation as well as females, the beds for the former sex being ultimately found in "Handel's" Ward. A second female ward, named after Mrs. Stafford, was now opened. A portrait of this lady is in the Hospital Board Room, with an inscription stating that it was presented by Mr. Joberns (surgeon from 1801 to 1832); tradition says that she was herself a victim of cancer. Another munificent benefaction, which enabled the Governors to still further extend the benefits of the charity, was that of Sir Joseph De Courcy Laffan, a physician, who died in 1848. By his will, which was proved on 15 February 1849, he desired that the residue of his estate should be devoted to the purchase of an annual income in the 3 per cent. Consols for the benefit of a cancer ward at The Middlesex Hospital. There appears to have been some litigation in connection with this bequest, and it was not until 22 February 1853 that the Chairman of the Board was able to announce that, except for costs of the suit, "the residue of Sir Joseph De Courcy Laffan's estate would appear to be £35,000 Stock and about £1900 cash." The three wards, "Whitbread," "Stafford," and "Laffan," containing twenty-six beds, for about fifty years occupied the uppermost floor of the central part of the main Hospital building, but in 1893 a scheme was initiated to transfer them to a separate building in Nassau Street. This resulted in the erection of the New Cancer Wing, which was opened for the reception of patients on 1 January 1900. It contains three wards of twelve beds each

and two smaller wards containing two beds each, whilst provision is made in a small operating room for any operations of emergency. The cost of the new block amounted to £19,693 14*s.* 6*d.*, of which £18,394 10*s.* 0*d.* was expended on building and £1299 4*s.* 6*d.* on furniture and general equipment. Prior to this notable extension of the department for cases of female cancer, fuller provision had been made for male patients. With this object the "Handel" Ward was remodelled in 1886 so as to give space for nine beds and a day room adjoining. The ward was renamed "Greenhow," after Dr. Headlam Greenhow (physician to the Hospital 1861 to 1879), who had been instrumental in obtaining funds for the endowment of male cancer beds.

Thus the cancer charity to-day consists of forty-nine beds, which are kept exclusively for cases of malignant disease in which no further relief by surgical operation is possible; and by the terms of the bequest founding the Cancer Fund, a patient, once admitted, is maintained in the wards "until relieved by art or released by death." No patient therefore is ever discharged from the cancer wards, except for mental derangement or insubordinate conduct. In accordance with the expressed wishes of many of those who have contributed in support of the Cancer Fund, the patients in these wards are under somewhat different general treatment to that which is appropriate to patients who are temporarily in the general wards of a hospital. Everything practicable is done to relieve the anxiety of their last days—that is to say, the diet provided is more varied than that ordinarily given to hospital patients, and less regard is paid to considerations of scientific economy in this respect. Pleasant sitting-rooms are provided for the use of such patients as are able, for the time, to leave their beds. The male patients are also allowed to smoke in their sitting-room. Every opportunity for seeing their friends and family is allowed the patients; and musical and other entertainments are provided for the patients at frequent intervals.

* * * * *

We may gather from Mr. Howard's writings that the main objects he had in view in proposing the foundation of a special cancer ward were these:—(1) To afford an asylum for life to

the distressing cases where, from the stage of the disease or its locality, no relief by operation or otherwise could be afforded. (2) To admit cases as in-patients where reasonable prospect of relief by operation could be given. (3) To establish an out-patient department for cases of a more chronic character, which could be suitably treated as such. (4) To keep records of every case under treatment, which records should be open to public inspection. (5) To institute trials of new methods of treatment, when properly authenticated. (6) To undertake scientific investigation into the nature of cancer.

During the century of its existence this charity has been conducted with more or less zeal on the lines laid down by its founder. Its primary object has undoubtedly been amply fulfilled. It has proved a safe and comfortable harbourage to many a shattered life, where the closing days have been spent in peace and in alleviation of cruel pains. Nor have its scientific objects been lost sight of, although at times mayhap they have not been followed with that absolute devotion that alone can be productive of real gain to knowledge. There have been times when this aim was almost lost sight of, or at least not given the prominence that it should have been. Nevertheless enough has been done by many of those connected with the Staff, who in succession have had charge of the wards of the charity, to considerably advance that which John Howard had in mind when he refers to Bacon, to Sydenham, and to Pott as exemplars of the true lines of surgical science and practice, and in this special field as shewing the way to unravel the mysteries of malignant disease.

It is but natural, perhaps, that more attention should have been given to the testing of remedies than the discovery of pathological processes. Mankind is ever impatient of the slow, if sure, progress made by the pursuit of the Baconian method of investigation. It cries out for results before the foundations of knowledge are laid, and would rather see blind attempts at "cure"—*ignes fatui* though they prove to be—than wait until research shall have demonstrated the only direction in which cure can be sought and obtained. And in such a disease as cancer, using the term in its widest sense, the opportunity for empiricism is ever present. Not that all so-called remedies that have from time to time been vaunted for the cure of cancer,

or indeed of any disease, are to be ranked on the same level. There is an honest as there is a base empiricism, and it is only as regards the former that anything need be said here, although this cancer charity did once have to deal with as arrant a quack as ever lived, and rectified its regulations accordingly. This was one Ashby, who professed by application of a certain remedy to extract from the cancerous tumour the "worms," which he maintained were the cause of the disease. He was introduced to the notice of the Hospital Board by the Hon. J. C. Villiers, who read a letter from Mr. Angerstein of Muddiford asserting that the remedy had been efficacious in several instances, and that "Mr. Ashby is anxious to apply it to the cancerous patients of this institution under the inspection of the medical officers." Ashby had the effrontery to appear before the Medical Committee and to agree to try his "remedy" in presence of the Staff, and also expressed his willingness to disclose its composition should the trial be satisfactory. This was on 5 April 1817; and on the next day (Sunday), the 6th, the Medical Committee again met and witnessed him apply his "remedy" to a cancerous breast. On the 7th they met again and discovered the fraud, which was stigmatized in no measured terms by Mr. (later Sir C.) Bell in a letter to the Board, expressive of indignation at such practices being permitted, "especially against a class of sufferers who demand all our sympathy."

Wilson ("History of Middlesex Hospital," p. 149) tells us that this disgraceful fraud led to the adoption of the following resolution:—

"That upon an application made by any person or persons stating themselves to be possessed of a remedy for cancer, and which they wish to be tried in the Hospital, it shall be a preliminary rule that the nature of the remedy to be made use of shall be communicated to the surgeon and physician under whose immediate care the patient may be upon whom the experiment is to be tried, in order that they may enable the committee to determine on the propriety of its application in the first instance, which would be the means of preventing an infinity of trouble to the medical officers, and perhaps render ineffacious the attempts to impose upon the public by persons stating that they are making use of a supposed remedy under the sanction of the medical officers of this institution, which circumstance has already occurred in two instances, namely, in that of a Mr. Green and Mr. Ashby."

Applications to try the effect of remedies were apparently very numerous in the first twenty years or so of the foundation of the charity; but many of these were refused, and not all were of the character of the one just referred to. It has already been stated that Mr. Whitbread, M.P., called the attention of the authorities to a mode of treating cancer by compression. The letter, dated Dover Street, 10 June 1815, forms the preface to a book entitled "Minutes of Cases of Cancer and Cancerous Tendency successfully treated by Mr. Samuel Young, surgeon, author of a 'Treatise on Cancer' and other Surgical Works." Mr. Whitbread says that the circumstances attending the foundation of the ward for the reception of cancerous patients in The Middlesex Hospital naturally led him to encourage every rational effort directed to the cure or alleviation of cancer; and having lately witnessed the happy effects of the practice of a surgeon, "known to the medical world by an approved 'Treatise on Cancer,' published before he had adopted the plan which he now pursues," he (Mr. W.) desires to "lay before you and the public the history of some of the cases which have been treated by Mr. Samuel Young since my acquaintance with him." He goes on: "Mr. Young received a part of his medical education in The Middlesex Hospital, and was for some time Surgeon to the House. He afterwards settled himself in the town of Montgomery. From that place, in the month of May 1814, he addressed a letter to me on the treatment of cancer. A correspondence followed, which ended in my request that he would come into Bedfordshire to give his advice to a near relation of my own afflicted with a disease called cancerous, and apply his mode of treatment if approved by the physician, whose opinion, from my long experience of his general science, talents, and liberality, I had determined to take." He then relates how he met Mr. Young at the house of Dr. Penrose at Hatfield, and "having received from the latter the most positive assurance that the plan could not produce any mischief, and afforded a prospect of relief, the experiment was decided upon, and on the next day it commenced at the residence of the patient, within a short distance of the town of Bedford, in the presence of Dr. Penrose and myself." Mr. Young then came to reside at Bedford, and the book contains the record of several cases treated by him, some of which were seen by Mr. Whitbread,

who says that he had "been more than repaid by witnessing the progressive amendment of the patients, and by hearing from time to time their joyful declarations that they were greatly relieved from the torment of their previous pain." Accordingly, Mr. Young's plan was tested in the Hospital, and we have from a highly competent authority, namely, Charles Bell, the results of that trial. It occurs as the first paper in his quarterly report, entitled "Surgical Observations," published in 1817. He bears witness to the great interest which Mr. Whitbread took in the cancer establishment and in every attempt to discover a cure for the disease, and praises the Governors for their zeal and liberality in the matter.

"Many proposals," he says, "are annually received by them for the cure of cancer, and always with that consideration which the motives of those who offer them deserve. But while our Governors have shewn themselves most desirous of promoting inquiry on the subject of cancer, they have remained uncontaminated by that love of quackery which is so common among the gentry of England, and have referred these proposals to their medical officers . . . . The recommendation of the plan of compression by Mr. Whitbread called the attention of the surgeons of the Hospital to the subject. The following report gives the result of their practice. I have only to observe that the essential part of this new plan of cure is the compression of the cancerous tumour, gently at first, and with a force gradually increased, till at last it is augmented to a very great degree; and that the means are these: if the cancer be open, the various holes and cavities are filled up from the bottom with chalk, finely levigated, and all the surface is thickly covered with hair powder; over this long plaster straps are put, so as to cover the whole surface of the tumour; over this again are placed linen compresses, bound down with the turns of a roller, firmly applied, and of six yards in length, or over the first straps are laid a second set bracing the parts more firmly than the first; over this a plate of lead, and lastly, the long roller is carried round the chest, compressing the whole."

The Report of the Medical Committee of 22 June 1816, giving the result of their experience of the method, was adverse. Eight cases of "open" cancer and eight of the "scirrhous kind" were subjected to the plan, which, in the former case, though sometimes lessening the volume of the tumour, often gave much pain and often appeared to hasten the end; and in the latter it did not retard the progress of the disease. Whilst

regretting that compression cannot be regarded as a remedy for cancer, the Committee believed that in many cases it produced alleviation. Mr. Bell, in a lecture on the subject, pointed out that the case which, according to Mr. Whitbread, was the most satisfactory, was one of ulceration of the lip, probably not malignant, and precisely of the character most likely to be benefited by a method securing perfect immobility. But in cases of cancer he shews that the specific action is not arrested by this means, whilst the compression may even hasten its progress and, in mammary cancer, accelerate the tendency of the growth to involve the chest-wall and lead to hydrothorax. He says that "the late Dr. Denman" believed in the efficacy of the method, but mentions cases of the class thought by that physician to be so curable in which an aggravation of symptoms was produced thereby.

Mr. Campbell De Morgan, referring to this plan ("The Origin of Cancer," 1872), gives it as an example of sanguine expectation ending in deep disappointment. "There is no doubt," he says, "that local improvement followed the use of pressure, and in some cases the tumours decreased in a remarkable manner. But there is great reason to believe that in some the spread of disease to internal organs was hastened." He gives the general conclusion of the Medical Committee, and adds that "at the request of Dr. Neil Arnott, Mr. Shaw tried the effect of elastic pressure by means of an india-rubber bag, capable of distension by air. But the general result was unsatisfactory, though in the first case it seemed to do good" (*loc. cit.*, p. 59).

About the same time as the above trials the Hospital Committee were invited by Dr. W. Lambe, F.R.C.P., to allow him to test the effect of his dietetic method of treatment in cancer. He was a rigid vegetarian, and believed that cancer was due mainly to an animal diet and also the use of impure water. He had written upon the subject, and submitted certain cases for investigation by the Committee in support of his views. However, after full consideration, the Committee were not able to recommend that any facilities should be given to Dr. Lambe for the trial of his treatment in the cancer wards.

Amongst the favourite remedies of "cancer-curers" in all ages has been the employment of escharotics, which have been vaunted as sufficient to destroy the morbid growth without the

application of the knife. Arsenic had been so employed for centuries. Its escharotic effects, says Spencer Wells,* "had been known to the Greek and Roman physicians—they had not been forgotten in the Middle Ages." It was the chief ingredient in the secret applications of Plunket and Guy, who flourished in this line in the first half of the eighteenth century. "It was Guy's caustic, or rather the Plunket's paste, that killed Lord Bolingbroke, and many others were poisoned by the local use of arsenic; yet this did not prevent Lord Arundel from buying the receipt of the wife of a blacksmith, so ignorant that she could not sign her name, but a noted cancer-curer, named Elizabeth Fellow. This was long known as 'Lord Arundel's Cancer Cure.' It was an arsenical powder and a wash of corrosive sublimate, and no doubt killed a great number of poor women. However, like Plunket's paste, a great many cancerous and other tumours were removed entire by it; and Mr. Justamond, who was Surgeon to the Westminster Hospital some seventy or eighty years ago, tried them both very extensively, arriving at the conclusion that the advantage gained did not compensate for the risk incurred." (Spencer Wells, *loc. cit.*)

In November 1852 an application was made to the Hospital Board by a Dr. Pattison of New York, to be allowed to test in the cancer wards the effects of a remedy which he had introduced. The application was refused, because he declined to reveal the nature of the remedies he employed. A few years later another New York physician, Dr. Fell, came to this country with similar pretensions, and, it is believed, with a "cure" for cancer not dissimilar from the secret remedies upon which his precursor had flourished. Unlike Dr. Pattison, however, Dr. Fell consented to reveal the composition of his remedies if he were allowed to apply them in the Hospital. This he did in the following terms:—

"1. That twenty-five cases shall be selected by the surgeons and myself (fair cases), and placed in my entire care in one of the wards of the Hospital until the disease is entirely removed and a healthy sore produced.

"2. The time to be occupied in the treatment of the said cases not to extend over a period of more than eight months, without the consent of both parties.

* "Medical Times and Gazette," 11 July 1857.

"3. That no person or persons shall see the cases while under treatment, except the surgeons and physicians of the Hospital, without my consent, and that no student, nurse, or other person shall be allowed to remove or interfere with my dressing.

"4. That the diseased masses, when removed, shall be preserved and kept in the Museum of the Hospital for at least one year.

"5. That, in the event of these conditions being satisfactory to the Medical Board and the Governors, I will communicate to the surgeons of the Hospital the remedies and plan of treatment pursued by me, upon their pledging themselves not to reveal or use the same without my consent until a period of six months shall have expired, when they shall have full power to do so. As I am about to publish a work upon the disease and its treatment, the above is simply to reserve to myself the power of throwing the treatment open to the profession.

"6. That, upon the conclusion of the treatment of the cases placed under my care in the Hospital to the satisfaction of the surgeons, I shall receive an acknowledgment to that effect from your honourable Board of Governors."

The Medical Committee, whose surgical members had, in common with numerous other medical men, "considered it their duty to inspect cases of cancerous disease which had been treated by Dr. Fell, and had witnessed effects of a kind hitherto unknown to them," advised the Board to accept the offer.* It was one made in accordance with the principles upon which such trials were alone permitted, namely, that the remedies could be used with safety, and that their composition should be made known as soon as they can be reasonably and fairly tried. And the Board, on 20 January 1857, resolved "That in concurrence with the opinion and recommendation of the Medical Committee of 19th instant, the proposal of Dr. Fell of New York, U.S., be accepted with all the conditions stipulated for. The Board desire further to tender to Dr. Fell their thanks for the liberal offer made by him to the Governors and Medical Officers of The Middlesex Hospital."

Six months later (16 June 1857) the Board passed the following resolution: "Resolved that, owing to the great interest taken by the public in the progress of the remedy for cancer now under trial in the Hospital, this Board wish to

* This decision was applauded by the leading Medical Journal, but as the trials proceeded, and the surgeons kept loyally to their agreement, they were violently attacked by the same journal for conducting a secret inquiry.

intimate to the Medical Officers that, as soon as they shall feel themselves at liberty to make a communication on the subject, this Board will be glad to receive a report of the number of persons cured or relieved by this remedy, and the opinion which the experience of the Medical Board may have led them to entertain of its utility and probable success."

Meanwhile, Dr. Fell himself had already published a book describing the method, which up to that time he had kept secret; and in this book he had inserted a sort of *ad interim* report which the Middlesex surgeons, with perhaps too easy complaisance, had drawn up in the previous March, or about two months after the trials commenced. They speak of the plan as one in accordance with known principles of surgery, as ingenious, safe and easy of application, leading to the enucleation of growths without destruction of healthy tissues, and followed by healthy granulating and cicatrizing surface. They admit that it is accompanied by pain, although this is variable in degree, and they did not think it was, on the whole, much less expeditious than cutting operations; but the brief time over which their observations had then extended did not permit of any conclusion as to the relative immunity of the two plans from recurrence of the disease. There is no word in this statement as to the nature of the means employed, and the publication of Dr. Fell must have somewhat forestalled the revelation made in the final Report, which was presented to the Weekly Board of Governors on 4 August, and by them recommended to the Quarterly Court to be published and circulated, "considering that this Report exhibits an anxious desire on the part of the Governors and the Medical Officers of the Hospital to carry out the objects and intentions of the beneficent Founder of the Cancer Establishment."

The Report, signed by the four surgeons, Alexander Shaw, Campbell De Morgan, Charles H. Moore, and Mitchell Henry, recites the main objects for which the cancer charity was founded, and the conditions on which remedies could be tried. It states that in the sixty-six years that had elapsed since the foundation many such trials had taken place, and many applications for trial had been refused on account of the promoters declining to comply with the condition that the nature of the remedies should be revealed. With respect to Dr. Fell's treat-

ment, the whole sum and substance of the Report goes to shew that, apart from its mode of application, it did not materially differ from long-established practices for removal of cancer by caustics. The caustic used by him was chloride of zinc, and his innovation consisted in the addition to it of a strong decoction of a herb, known to the American Indians, called "*sanguinaria,*" an ingredient which, as a matter of fact, might just as well have been dispensed with. It was, however, considered by Fell to have specific properties, for, besides using it in the local applications, he prescribed it internally to every case, in the belief that it counteracted the cancerous tendency. During the trials, which lasted over a period of eight months, some sixty cases were treated, some being cases which were suitable for operation by the knife, others in which such a procedure would have been inadmissible. Nearly all the cases were cancer of the female breast or skin. The local treatment consisted in first destroying the skin (when this was not already ulcerated) by means of nitric acid, and then inserting the "paste" into shallow incisions made into the substance of the tumour, the paste being spread on strips of linen, and the applications renewed day by day, with deepening of the incisions, until the whole of the diseased mass had been subjected to the action of the caustic. It is hardly necessary to enter here into further detail; for that the reader may consult the original Report.* Suffice it to say that the conclusion was on the whole a favourable one. To be sure, it disallows the claim that there was any specific property in the drugs employed, or that the caustic was limited in its action to the cancerous growth, whilst in some cases the irritation it caused seemed to excite the disease to rapid extension. The pain, especially in the earlier process of destroying the skin, was often severe, and again at the close, when the sloughing mass was becoming detached from the subjacent living tissues. The surgeons did not, however, consider that the pain was of such severity as to outweigh the advantages of the treatment. They point out that the plan has one notable advantage over the use of the knife, in that it can be applied in

* "Report of the Surgical Staff of The Middlesex Hospital to the Weekly Board and Governors upon the Treatment of Cancerous Diseases in the Hospital on the Plan introduced by Dr. Fell." Printed by order of the Quarterly Court (London: Churchill. 1857.)

cases which are beyond the reach of that mode of extirpation; and, as regards those cases to which either method is applicable, they seem to think that the escharotic plan may well be preferred, although unable necessarily to aver that there is any difference in the two methods in respect to liability to recurrence of the disease. They shew that the practice of inserting the caustic into the growth by means of incisions, although involving a longer period for the complete extirpation of the tumour than does the usual method of application of caustics, may be an advantage in causing less irritation and excitation of local cancerous action. The addition of sanguinaria was of no practical value, its escharotic power being practically *nil*. Finally they say:—

"The last peculiarity of this treatment is the practice of incisions, and we are of opinion that this is its only, but its very great merit. The sanguinaria is inert—the chloride of zinc paste was known before—but the incisions constitute a new feature in the treatment of cancerous tumours, for which we find no parallel in the writings of the past or in the practice of present surgeons. Cancer in its constitutional nature remains as ruthless and as unassailable as ever. Chloride of zinc may not continue to be used for the destruction of the local disease. But the advantage placed in the hands of surgeons by the invention of gradual incisions claims henceforth their very frequent adoption in the treatment of cancerous tumours, as well as a grateful acknowledgment of the ingenuity of their inventor."

This does not seem to be a very great result of the trial of a remedy vaunted to be an unfailing "cure" of cancer, and there were not wanting critics who pointed out that even the practice praised by the reporters for its ingenuity was not so novel as they deemed it to be. To us the lesson of this inquiry lies in the demonstration that the remedy, of which so much had been expected, which had long been kept a secret, was found to be no remedy at all; and the fact that the practice of removal of growths by the slow and painful plan of mineral cauterization has not become established, except in isolated instances where no other procedure is available, goes to shew that the hopes excited by this plan were soon falsified, and another method consigned to the limbo of discarded cures of this baffling disease.

The chapter of this experiment, so far as concerns the Hospital, was closed in the letter addressed to Dr. Fell in accordance with a condition agreed upon when he entered upon the treatment of cases in the cancer wards:—

"Middlesex Hospital,
"22 September 1857.

"Sir,

"The period of eight months proposed by you for your attendance upon some of the patients in the cancer wards of the Hospital having now expired, the Weekly Board has much pleasure in presenting you with an acknowledgment that you have fulfilled all the conditions under which you undertook to give the patients the benefit of your services.

"The Weekly Board being composed of gentlemen not connected with the profession of medicine, and therefore not feeling from their own observation competent to pronounce any opinion as to the value of the method of treatment peculiar to you, refer to the judgment expressed on that point by their Surgical Staff in the elaborate report, which is now being circulated amongst the Governors of the Hospital and the members of the profession. They rely with the utmost confidence on the terms of this report. They are glad to observe that your treatment is considered by those who have so carefully watched it for the past eight months as possessing important advantages over methods previously in use. They are led to believe that it affords facilities for eradicating the local cancerous disease in cases hitherto considered almost hopeless, and they are themselves aware that many of the patients who have been subjected to it have warmly expressed their gratitude for the benefits conferred on them.

"The Weekly Board has witnessed with great satisfaction the regularity of your attendance and your uniform kindness and consideration for the sick.

"I am, etc.,
(Signed) "MICHAEL SMITH,
"Chairman of the Weekly Board.

"To J. WELDON FELL, M.D."

There is preserved in the Hospital Museum (No. 2114) a specimen of "a breast removed *en masse* for cancer with Fell's paste. There are nine parallel incisions extending through the gland. The posterior surface is smooth." The entry in the Catalogue further states, "The growth was, by permission,

removed by Mr. Fell from a patient in the cancer wards. It returned in the cicatrix of the wound twenty-two years afterwards and proved fatal."

Dr. James Arnott in the same year (1857) applied for and obtained permission to test the effect of a plan he had devised of treating cancerous growths by freezing. The plan was said by Spencer Wells to be "really of great service . . . .; it allays pain, checks growth, and has reduced many large adherent tumours to a small, movable, indolent condition" (*loc. cit.*). Mr. Campbell De Morgan, writing in 1872, says of this method: "The cold has been applied by putting a mixture of ice and salt into an ice-bag and keeping it over the tumour. In this way the tissues may be destroyed to a certain but limited extent. The cake of frozen tissue which is formed seems to protect the parts below from the full influence of the freezing mixture. It might answer in small superficial tumours, but here other modes would be simpler and more certainly effective. The plan was tried at The Middlesex Hospital on the suggestion of Dr. James Arnott."

It need not be said that new lines of treatment have often been employed for cancer in these wards without any application from outside. The surgeons in charge have always been alive to the progress of science, and many a plan has been put in operation, often, indeed mostly, with the result that it has been found wanting in respect to the permanent cure of cancer. It is true that now and then an apparent success has been gained, but a repetition of trials has shewn this to have been exceptional, and perhaps explicable on the rare, yet occasional, tendency of the disease to spontaneous recovery. Amongst methods involving the internal administration of drugs there are two that may be briefly noticed.

The bark of Condurango, a plant belonging to the Asclepiadaceæ, many of whose members are used medicinally, is indigenous in Ecuador. It had been known to have been used in the treatment of cancer, and had been tried at The Middlesex Hospital in consequence of the claims advanced for it by Dr. Cascares, surgeon to the hospital at Quito, namely, that when administered internally it caused scirrhous induration to soften, the tumour to dwindle and disappear, to improve and ultimately to heal ulcerations, to improve digestion, and restore

health. A fair trial was given to this remedy in 1871-2 in the cancer wards by the late Mr. Hulke and Mr. De Morgan, who related the results of their experience, which were wholly negative, at a meeting of the Clinical Society of London ("Clinical Transactions," vol. v., p. 115, *et seq.*). There was not the slightest evidence that any effect at all had been produced by the administration of the remedy.

Precisely similar negative results followed trials with Chian turpentine, which was introduced to notice as having a remarkable effect in checking the growth of uterine cancer, by Mr. Clay of Birmingham, in 1880 ("Lancet," 1880, vol. i., p. 477, and vol. ii., p. 533). Mr. H. Morris (*ibid.*, 1880, pp. 844 and 886) and Mr. Hulke (*ibid.*, 1881, vol. i., p. 1019) arrived at a precisely opposite conclusion to Mr. Clay, as the cases they detail justified them in doing. The subject attracted much attention at the time, and whilst one or two writers confirmed Mr. Clay's results, others concurred in the verdict of the Middlesex surgeons. In 1886 Mr. Clay reiterated his belief in the efficacy of the drug, but, so far as I am aware, it has never come into general adoption.

It is not necessary to dwell at length upon a record which is full of failure as this of the vain attempt to find in some fortuitous way a specific for cancer. It is a chapter of medicine of which we can hardly be proud, and contains perhaps more of folly and disappointment than any other.

"A multitude of strange remedies are prescribed for cancer. When Lord Metcalfe, the Governor of Canada, was beset with this cruel disease, Mr. Kaye, his biographer, tells us: 'One correspondent recommended mesmerism, which had cured Miss Martineau; another, hydropathy at the pure springs of Malvern; a third, an application of the common dock leaf; a fourth, an infusion of couch-grass; a fifth, the baths of Docherte near Vienna; a sixth, the volcanic hot springs of Karlsbad; a seventh, a wonderful plaster made of rose-leaves, olive-oil, and turnip juice; an eighth, a plaster and powder, in which some part of a young frog was a principal ingredient; a ninth, a mixture of copperas and vinegar; a tenth, an application of pure ox-gall; an eleventh, a mixture of Florence oil and red precipitate; whilst a twelfth was certain of the good effects of homœopathy, which cured Charlotte Elizabeth. Besides these varied remedies, many men and women with infallible receipts or certain modes of treatment were recommended

by themselves and others. Learned Italian professors, mysterious American women, erudite Germans, and obscure Irish quacks—all had cured cancer of twenty years' standing, and all were pressing or pressed forward to operate on Lord Metcalfe.'" (John Timbs, "Doctors and Patients," 1876, p. 338.)

Surely the experiences that have been gained in the treatment of this disease, and the multiplicity of remedies that have been advocated for conditions which remain incurable, must impel the conviction that it is not by haphazard guesses that a cure will be found. We may well revert to the words of Sydenham, quoted by John Howard in the letter he addressed to the "medical gentlemen of the Hospital," with which this article opens, as shewing the direction in which we have to go.

"I have often thought that if I knew accurately the natural history of any disease, I should never be at a loss for a proper method of treating it." In giving this quotation there is no doubt that Howard saw the importance attaching to the study of a disease like cancer in order to determine its nature before any real advance could be made in treatment. He felt, as we have seen, that investigation was what was needed, and both he and his friend were of one mind upon the scientific as well as the philanthropic side of the institution. They were far-sighted enough to perceive that in point of fact the benefits conferred on the community by the foundation were not restricted to those who were relieved in its wards, but they hoped, and not without reason, that the experiences gained by those who ministered to them would lead to a wider and sounder knowledge of the disease and its relations. Therefore, we have stated that one of the objects which were in the mind of the founder when he made his benefaction, just as it was in the mind of Mrs. Stafford when she penned her will ("curing persons afflicted with cancer, and of investigating and promoting our general knowledge of treating that dreadful disorder"), was to gain a greater insight into its nature, so as the more certainly to discover the means of successfully coping with it.

* * * * *

In the century that has elapsed since this cancer establishment was founded, there has been a very considerable extension of knowledge concerning the nature and structure of the morbid conditions collectively termed "cancer." To this work many

contributions have been made by surgeons who have had charge of this department. John Howard, the first to hold this position, left behind the manuscript of a work entitled "Practical Observations on Cancer," which he placed in the hands of Dr. Gower, Physician to the Hospital, by whom the publication was undertaken in the year of Howard's death—1811. Many of the cases described in the book were inmates of the cancer ward, regarding which, Dr. Gower, in the preface addressed to John Morris, Esq., and William Fowler Jones, Esq., Treasurers to The Middlesex Hospital, states: "Through the munificence of the late Samuel Whitbread, Esq., an asylum appropriate to females afflicted with the disorder in question was first established, a cancer ward having been opened in The Middlesex Hospital by the unremitting exertion of his friend Mr. John Howard."

It is not very easy to gather from a perusal of its pages any very clear ideas as to the nature of the disease of which it treats. This is in part due to the form in which it is cast, and probably also to the lack of that "amplification and revision" which the editor regrets that the author was prevented by a tedious illness from bestowing. It consists of a congeries of clinical records interspersed with general reflections, and, although apparently intended to be drawn up on a system, is yet sadly unsystematic. The main doctrines one is enabled to gather are these: 1. That cancer occurs in many forms, and that many simple diseases have been confounded with cancer. 2. That persons who in early life have been "scrofulous" are liable, as age advances, to become the subjects of cancer. 3. That the proclivity to cancer in the decline of life is favoured by the tendency to venous congestion that then occurs. 4. That cancer is a disease of glands. 5. That scirrhus is the first stage of cancer. 6. That cancers may arise from blows and injuries as well as from internal causes. 7. That if a cancer be not removed early, before it becomes adherent, the constitution is liable to be affected by the virus generated within it. 8. That excision by the knife can only be safely done in the scirrhous stage, with caution and a "very guarded prognostic," when the growth has increased so as to cause the skin to become tense, and not to be attempted when the cancer has become adherent to deeper parts and the skin has commenced to ulcerate.

9. Cancers may be chronic or acute; in mammary cases minute nodules may spread into the surrounding skin, lymphatic glands may be indurated by passage of fluid from the cancerous breast, but it is unwise to remove these glands as swelling of the arm is sure to follow. 10. In all cases there is a predisposing as well as an exciting cause; injury will not produce cancer unless there be predisposition, and this latter may be inherited, just as the scrofulous habit is hereditary. 11. Partial or imperfect removal of a cancer is followed by fresh sprouting; indeed, even when the whole of the diseased part has been apparently removed, there may remain behind "semina" or "roots" so small as to escape recognition, but sufficient to explain the local recurrence that follows.

Speaking of cancers of the lip, he notes their greater frequency in men, and the editor, in a note, says that this "disposition in men of the lower orders of life *may* have its origin in the habit of smoking tobacco, which produces the liability to *irritation* on that part from the accidental adhesion of the tobacco-pipe." Another instance of such local irritation is afforded by the author in his remarks on "a species of cancer which is very common to a body of people who are greatly to be pitied, namely, *chimney-sweepers*." This begins as a "soot-wart," and the irritation of this leads to its becoming cancerous.* Mammary cancer furnishes him with the greatest number of examples. Here is his comment on one where the disease recurred locally within seven months of excision, and where, after a second operation, an interval of nearly as many years occurred before death, which was preceded by lymphatic infiltration and probably internal dissemination. He says:—

"It is a very interesting case. The second tumour, arising on the cicatrix so soon after the removal of the breast, shews that a portion of disease was left behind and produced its regeneration; and the rise of the small tumours, after the second operation, points out that there were germs remaining, which were the occasion of others being multiplied to such an extent that the disease ended in death. The whole progress of the tumours demonstrates, in my opinion, a *local glandular sympathy*, and seems to shew that there was no absorption of matter into the system from the first and second tumours, nor from

* In his previous "Notes and Observations" Howard remarks that in two cases of this affection the disease arose from "wood soot and that only."

the three last, before ulceration; and, if so, the disease, whilst in such states, may be said to be *local*. If the disease be propagated by a germ, or one diseased gland, it may be like a seed planted in the ground, having a local action where sown, and extending only to a certain space, without influencing the whole of the system."

Words worth remembering when we consider how, many years later, there was much debate as to the local origin of cancer. He goes on to say:—

"There are three things of great consequence to determine, namely: first, at what period of time in the disease the acrimonious fluid of a cancer can be absorbed into the system of the person affected; 2ndly, whether it be not sometimes a disease merely local; and 3rdly, whether, although appearing as a local affection, it may not be a disease of the constitution, like scrofula for instance, which is not a local but a general disease, although it may exhibit itself in one place only.

"This case I noted more than twenty-eight years ago. At that time the great utility of purgatives and issues I did not know, nor were they attended to by medical men. I make no hesitation in saying that had I known so much then there would have been a great probability of prolonging this person's life, after the appearance of the three small tumours, beyond the period of seven years from the second operation—a want of knowledge I shall regret to the last moment of my life" (p. 99).

It may be questioned whether the use of "purgatives and issues" would have averted the course of the disease, which has often had its parallels, the case being an illustration of the remarkable "latency" of cancer, which is so difficult to explain on any theory. Many an instance has been recorded of recurrence at even longer intervals than in this case, over which John Howard had such unavailing regret, and it may safely be said that no remedies known to medicine possess the power of preventing such a recrudescence. We may also quote the following brief narratives of cases, the second of which exemplifies the fact, frequently experienced in its history, that not every case treated in the cancer ward has been a case of cancer:—

"Case 45.—A cancer in one breast was removed by the late Mr. Wyatt, and a like affection went afterwards to the other, which induced Mr. Wyatt to refuse performing a second operation. She left The Middlesex Hospital, and this breast was taken off out of the

house by another surgeon. At no great length of time from the last operation a scirrhous affection of the liver took place, of which she died, it having been found in this state upon dissection" (p. 101).

"CASE 48.—A woman, aged 24, had an ulceration in the axilla, the origin of which was what she called a lump. It was seven years increasing in its progress to its present state of ulceration, and it had been ulcerated a year and a half. She had also a fulness and tumour under the clavicle of the same side. This case was strictly scrofulous, and was cured by the external application of Wiltshire Holt Water" (p. 103).

The mention of "Wiltshire Holt Water" in the last case will probably puzzle the modern reader. It was at that time a favourite local application to ulcerated surfaces, being often mentioned in these pages. It appears that in 1718 a mineral spring was discovered at the village of Holt, near Bradford-on-Avon,* but as the most recent gazetteer is silent on the subject it may be inferred that, like many another English spring, the well has run dry. As to its reputed virtues, it seems somewhat singular that Mr. Howard should have retained his faith in them in view of the following instructive anecdote that he relates in a footnote (p. 102):—

"Some few years ago I was informed that a young gentleman, who acted as House Surgeon at the time to The Middlesex Hospital, had omitted to procure a supply of the Wiltshire Holt Water, which was in much request. To conceal the circumstance he filled one of the accustomed bottles with water from a pump in the apothecary's shop there, and having inserted a sealed cork to complete the resemblance, he used that water as a substitute. The effects were so similar to those of the genuine mineral water that he continued to employ it, and to gain instruction in his profession." And the writer adds: "Of the truth of this relation I have no doubt, and I therefore feel it to be a duty to record it."

Amongst other local applications mentioned the carrot poultice was much in favour, but one of "red onions" (mashed and cold) seems from the records to have been mostly too irritating.

It is time to leave John Howard and his book, which has now but little more than an antiquarian interest. We must,

* "Imperial Gazetteer of Great Britain," *circa* 1865. See also "An Account of the Nature and Medicinal Virtues of the Principal Mineral Waters of Great Britain and Ireland, etc.," by John Elliott, M.D. (1784, second edition), p. 187.

however, note that he was thoroughly imbued with the great principle of the early and free removal of malignant growths. "The removal," he says, "cannot be too early nor too perfectly done without attempting to save the integuments, as has been too frequent, or the parts immediately surrounding the tumour or attached to it posteriorly .... Every the smallest portion of diseased hardness must be therefore taken away, leaving the parts surrounding the tumour, in every direction, in a sound state. When this rule of practice has been followed, the cure has very frequently been complete and lasting; but when it has not been sufficiently attended to, the cure has too often failed." He recognized also the value of opium and lead as local sedatives, and lays stress on the advantage of an abstemious regimen, for he had observed that cancer progresses far more slowly in the abstemious than in those who indulge themselves and lead indolent and luxurious lives. One final passage may be quoted in which he gives his opinion on specifics:—

"Much has been said and much expected of medicines of a *specific* nature for the mitigation and cure of cancer, but this object, in my humble opinion, is not likely to be attained by any one medicine, but by the co-operation of several, uniting to form and support different indications according to the state, nature, and circumstances of the various affections which go under the general name of Cancer" (p. 126).

We may take a glance at a contemporary work on the same subject, in the hope that it will give additional insight into the doctrines held by scientific men regarding cancer in those days. There is the work entitled "Observations on Cancer," by Everard Home, published in 1805, a work which, it is not too much to believe, contains the views, if not the *ipsissima verba*, of John Hunter, at whose death in 1793 the priceless collection of manuscripts on a variety of subjects in natural science and surgery came into the hands of Home, who, as all the world knows now, ruthlessly destroyed them after having, so it is also firmly believed, made much use of their contents in the preparation of his own works. Nor indeed does Home conceal the fact that much of this book on cancer is Hunter's, for in the ninth chapter, which deals with the Nature and Progress of Cancer, he writes: "In stating these observations, I wish it to be understood that I am communicating all the material infor-

mation I have been able to collect upon this important subject, and not meaning that it should all be considered as my own. Much certainly originated with Mr. Hunter, perhaps the greatest part . . . ."

Therefore it may be inferred that the view herein stated, that "cancer is a disease which is local in its origin," was that held by the foremost of British pathologists. This statement is followed by one to the effect that cancer cannot arise in any part unless that part has undergone some previous change. This is illustrated by the well-known facts of small cutaneous growths remaining for many years harmless, until in advancing age they are excited into cancerous activity by some irritation or injury. Nor are these views considered to be incompatible with the hereditary transmission of cancer, it being the disposition and not the cancer that is inherited. It may be that the disposition does not appear until late in life, but then, from some slight cause, a tumour may form, within which, as it increases, "cancerous poison" may be generated.

In the following passage Home declares the purpose of his work :—

"The object of the present observations is only to promote the investigation of cancer, as a disease, in the knowledge of which a very small progress has hitherto been made, and till that knowledge shall be more advanced, nothing can be said respecting the mode of treatment to be recommended in confirmed cancer, unless some fortunate accident should be the means of our discovering a remedy. Till we arrive at a more perfect knowledge of the disease, or till such a discovery shall be made, it becomes of no small importance to ascertain in what way these tumours can be dispersed, which, if allowed to remain, too often become cancerous, or, when their dispersion cannot be effected, what is the best mode in which they can be removed ; for I am induced to believe from what has fallen under my observation, in the practice of Mr. Hunter, and afterwards in my own, that when the cancerous poison has acquired the power of contamination the disease is generally too far advanced to be subdued by the extirpation of the tumour" (p. 152).

It must be admitted that there is not, in essence, very much difference between the conceptions of the disease to-day and those held by the two writers just quoted, separated as they are from us by the whole of the wonderful nineteenth century, during

which pathology, like all other of the sciences, has made such notable advance. Allowing for differences in modes of expression, can we not say with the one writer that in cancer there is a predisposing as well as an exciting cause at work? and with the other, that cancer is a disease which is local in its origin, but that it seems to require some special disposition, which may be inherited, to evoke it? In the memorable discussion at the Pathological Society in 1874, Mr. Campbell De Morgan, who more than any other upheld the doctrine of the local origin of cancer, was fain to admit "that though local in its origin there is in some, possibly in all, cases a predisposition to the disease, which may possibly be distributed through the system, but which more probably has its seat in some one among the tissues of the body." And Sir James Paget, the powerful defender of the "constitutional" view, entirely endorsed this statement, which seemed to him to grant much of the thesis that he was himself maintaining. Further, we find that at the beginning, as at the close of the century, surgeons were equally impressed with the necessity for early removal of cancerous growths, and with the liability to recurrence which imperfect operations suffered to occur. John Howard's surmise that "seeds" or "germs" not visible to the unaided eye are left behind after such partial excisions is a literal fact, which the application of the microscope has verified. It is only when we endeavour to realize what the surgeons of that day really knew of the nature of cancer, and of the confusion that evidently existed in their minds in respect to its supposed relationships with scrofulous, syphilitic, and leprous affections, that we are enabled to gauge the extent to which knowledge has advanced since their time. Setting aside the errors into which they fell with regard to the morbid conditions just named, we find their conceptions of cancer itself to be singularly strange. No longer can we speak of "scirrhus" as a sort of precursory stage of true cancer, and include under that term such conditions as cirrhosis of the liver and uterine fibroids. We may well doubt, too, if there is any proof for the assertion that when the cancer attains a certain stage it generates a virus, to which is ascribed the destructive progress and general dissemination of the disease. Nor can it be said that the belief in injury as an exciting cause has so firm a hold upon the imagination as it had

in those days, although the undoubted fact that cancer does in some cases ensue upon injury has justly been regarded as one of the strongest arguments in favour of there being an underlying constitutional tendency to the disease in those who suffer from it.

Unquestionably, the main reason why the pathologist of to-day has more precise notions concerning cancer than had Hunter or Baillie is almost wholly due to the extent to which microscopical investigation has been applied to the study of morbid growths. The earliest steps in this direction nearly led the scientific world astray, and for a time the specific cancer cell was eagerly welcomed as solving the mystery that shrouded the subject. But as a knowledge of the constitution of the normal textures of the body became more exact, and when to histology was added the light thrown on the developmental history of the organism by the new research in embryology, the pathologist had to discard a doctrine which had been too lightly embraced. He came to recognize that the cancerous neoplasm was composed of elements akin to those found in normal tissues, arranged, it may be, on an irregular pattern, and met with in localities where normally such cells do not occur. Then came the great differentiation between carcinomata and sarcomata, the one built up on the type of epithelial and glandular elements, the other on that of connective tissue—a fundamental distinction in structure, reaching back to the primary differentiation of the embryonic layers. The outcome of all these studies upon morbid growths, to which Virchow's masterly treatise contributed so largely, and the furtherance of which was one of the main objects of the Pathological Society of London, founded in 1846, needs not to be related here. Suffice it to say that little now remains to be done in this direction. The minute structure of such growths, the common sites of their origin, the essential distinctions between benign tumours and malignant, the accumulated evidence concerning the lines of infection and dissemination of secondary growths—these and numerous other facts concerning them have brought us nearer to that full knowledge of the "natural history" of the disease which Sydenham rightly deemed to be the foundation of correct treatment. In this advance to clearer knowledge the surgeons who have in succession had charge of the patients

of Whitbread's charity have borne their part. It would be invidious to name any who are still with us, but the work done by De Morgan, Moore, and Hulke, both in respect to pathology and treatment, should not be forgotten. The Hospital records have, too, been of value in furnishing trustworthy statistics on the subjects of heredity, of relative frequency and distribution of cancers, of duration, the results of operative interference, the liability to recurrence, and other matters which have all to be reckoned in contrasting present knowledge with that of the eighteenth century. In connection with this statistical side of the question, mention should be made of the contributions of the late Mr. Sibley, who for many years held an office corresponding to that of Surgical Registrar, whilst the published reports of those who have held that office furnished annual statistical and other records of the department for thirty-three years.

* * * * *

The opening of the New Cancer Wing, besides increasing the accommodation and comfort of the patients, has afforded an opportunity to establish laboratories for the systematic scientific investigation of cancer, thus fulfilling in the most satisfactory manner one of the main objects for which the institution was founded. For in spite of the more exact knowledge of the morbid anatomy of cancer that is now possessed, the important problem of its causation remains almost as obscure as at the date when The Middlesex Hospital accepted Samuel Whitbread's gift. The discoveries of the past twenty-five years in respect to the causal agencies of many of the zymotic diseases, and especially of tuberculosis and malaria, have raised hopes that somewhat similar agencies of a parasitic nature may ultimately be found to be at the root of malignant disease. At any rate the time has arrived when, equipped with the best available methods, a determined effort should be made to unravel a mystery that has baffled the wisest. This can only be through the most assiduous and careful study embracing a very wide field.

The new departure at the Hospital was marked by the constitution of a Cancer Investigation Committee, consisting of the senior Physician to the Hospital, the three Surgeons, and the Lecturers on Medicine and General Pathology. A Director

was appointed to control the Research Laboratories instituted in the new building, together with a Pathological Assistant and a Resident Registrar, whose duty it is to take charge of the wards under the surgeons, and to keep the clinical records. Mr. A. G. R. Foulerton was appointed Director, and Mr. W. T. Hillier Pathological Assistant. The office of Registrar, at first filled by Mr. Clifford, is now held by Mr. J. Myler.

The laboratories were opened on 1 March 1900. The material at the disposal of the department in each year comprises that from about 250 cases of malignant disease (not counting cases of recurrence). In connection with the special cancer wards, from seventy to eighty post-mortem examinations are made every year, these being carried out by the Staff of the Research Laboratories. The general wards of the Hospital contribute about twenty post-mortem examinations of cases of internal malignant disease, and material from about 150 cases operated on in the surgical wards. As complete an examination as possible is made of every case from which material becomes available, and it is hoped that the systematic recording of cases on an uniform plan may in time produce results of value.

Reports will be issued from time to time by the Cancer Research Laboratories, the intention being that each Report shall, as far as possible, deal with a series of 500 cases of malignant disease completely examined. The Reports will also contain a series of papers embodying all original work bearing on the pathology of malignant disease carried out by the Staff or by voluntary workers in the laboratories.

The present Volume is the fulfilment of this intention.

In establishing the Cancer Research Laboratories the Governors of The Middlesex Hospital have not only been faithful to the trust confided to them, but they have set an example to others similarly engaged in the warfare against disease. They have perceived that the only sure foundation upon which successful treatment can be based is that of knowledge of the nature and causes of diseases. In such investigations as can alone be carried on into the difficult and complex problems of cancerous affections, it may be long before any decided practical result can be attained. But the labour will not be thrown away. Every additional fact, however small, will contribute to the better understanding of the

conditions under which such diseases arise and the manner in which they spread. That in due time such knowledge will be the means of directing us where to look for the means of checking and preventing cancer there can be little doubt. Such a consummation will, however, only be attained by the exercise of unwearied patience and assiduity by those engaged in the task.

As indicating the nature of the lines of investigation at present suggested by modern knowledge, I cannot do better than append the scheme of the "Scope of Investigations," which was presented to the Medical Committee by Mr. Fouler-ton before the Laboratories were opened:—

SCOPE OF INVESTIGATIONS.

1. A systematic bacteriological and histological examination to be made in every case of Carcinoma or Sarcoma admitted into the Medical, Surgical, or Special Cancer Wards of the Hospital, or dying in the Special or General Wards. The results of this systematic examination would be applied:—

(1) To the attempt to formulate a satisfactory classification of Sarcomata.
(2) To the investigation of the causes of Carcinoma and Sarcoma.

A. Whilst a satisfactory histological classification of the varieties of Carcinoma has been in use for many years, the classification on the merely histological basis is still far from complete in the case of Sarcomata.

B. With regard to causation.—In the case of Carcinoma recent theories as to a blastomycetic causation require investigation. Although the theories in question have not been generally accepted, the arguments in favour of them have been very ably urged by Italian pathologists, and careful bacteriological examinations are required, if only for the purpose of obtaining negative evidence.

The theory of a Protozoal causation has now been practically abandoned by pathologists, and probably would not require any further investigation.

The older theory as to the direct origin of Carcinoma from normal epithelial cells as the result of a perverted or irregular

overgrowth, and independently of the influence of any parasites from without, would seem to offer the line of research from which definite results might most probably be expected.

c. With regard to the Causation of Sarcoma.—Our knowledge of the pathology of Sarcoma is even less definite than it is in the case of Carcinoma. We have reasonable grounds for assuming that all varieties of Carcinoma are, at any rate, manifestations of one and the same kind of morbid action. But with regard to Sarcoma there is reason to believe that the term, as ordinarily used, includes the results of more than one morbid process. Recent investigations (Curtis, Busse, and Nello Biargi) have shewn that some of the cases which clinically might be classed as Sarcomata are definite instances of yeast infection. And there is also presumptive evidence that some of the cases which are clinically recognized as "lympho-sarcoma" may similarly be caused by a parasitic infection of some sort.

On the other hand, there is no reason for supposing that all cases of Sarcoma are due to a parasitic infection. And the relation in some cases of Sarcoma to chronic inflammatory processes, arising independently of the action of micro-organisms, would require investigation.

d. An exact tabulation, founded on histological data, of Carcinoma and Sarcoma cases, with regard to the age and sex incidence of the two diseases, would be of great value in connection with Public Health statistics. In the Registrar-General's Returns the term "Cancer" is used as including both Carcinoma and Sarcoma, and there are at present no means of ascertaining the relative frequency of each. This use of the word "Cancer" is necessary because of the difficulty of exact diagnosis in many cases as they occur in practice.

But these "Cancer" statistics, including as they do the Returns of at least two diseases, are at present almost valueless when investigating the influence of general surroundings and the like in the causation of either of the diseases. By the systematic recording of a considerable number of cases of Carcinoma and Sarcoma it would in time be possible to construct tables shewing the exact age and sex incidence of the respective diseases. And such tables might throw much needed light on the Registrar-General's Returns of "Cancer" for the whole country.

2. Systematic examination of the blood (leucocyte staining and enumeration) in series of selected cases of malignant disease, before and after operation and also in inoperable cases, is a line of research which might afford useful data which could be applied to clinical diagnosis in doubtful or obscure cases.

* * * * *

It is somewhat remarkable that almost coincidently with the step taken by The Middlesex Hospital authorities to promote scientific inquiry into cancer, committees having the like object in view should have been founded in Germany and the United States, whilst there already exist certain "leagues" against cancer in France, Belgium, and elsewhere.

In Germany there was founded in 1900 the "Deutsche Comité für Krebsforschung," with Professor Geheimrath von Leyden as President and Professor G. Mayer as Secretary. The meetings of the Committee are held monthly in the "Ministerium des Inneren," the Committee receiving an annual subsidy from the Imperial Exchequer of 5000 marks. The Committee, whose members comprise professors of medicine, physicians and surgeons, bacteriologists, morbid anatomists, veterinarians, etc., has no special laboratories, but administers funds in grants to those engaged in research, and collects statistics.

There are also two special laboratories in Germany devoted to cancer investigation: (1) The one is attached to the clinic of Professor von Leyden at the Charité Hospital in Berlin. There is a special ward for cancer, containing thirty-four beds, with a laboratory, both being under Professor von Leyden's direction. The ward is maintained by the State, the annual charge being 53,000 marks. (2) The other is the Cancer Laboratory at Frankfort, which is privately supported, and of which Professor Ehrlich is the Director.

In the United States there are laboratories at Buffalo and Harvard. The laboratory at Buffalo was placed formally under the control of the New York State Department of Health in June 1901. Dr. Roswell Park is Director, and the Staff includes a pathologist, a clinical microscopist, a bacteriologist, and a chemist. The laboratories have lately been extended considerably, and removed to a building presented by Mrs. Gratwick.

The Cancer Committee to the Surgical Department of the Harvard Medical School, Mass., U.S.A., is endowed with funds bequeathed by Caroline Brewer Croft. The Committee have organized a commission of workers, who presented their first Report, containing Papers dealing with the Pathology of Malignant Disease, on 23 October 1900.

Finally, the present year (1902) has seen the formation in this country, under the auspices of the Royal College of Physicians of London and the Royal College of Surgeons of England, of what may be regarded as a National Committee for the promotion of Cancer Research, the aim being to raise a fund sufficient for the complete prosecution of this work. The objects are succinctly stated—(1) To provide, extend, equip, and maintain laboratories to be devoted exclusively to Cancer Research; (2) To encourage researches on the subject of Cancer within the United Kingdom, or in the British Dominions beyond the seas; (3) To assist in the development of Cancer Research Departments in various Hospitals and Institutions approved by the Executive Committee; (4) And generally to provide means for systematic investigation in various other directions into the causes, prevention, and treatment of Cancer.

NOTE.

The early history of the Cancer foundation at The Middlesex Hospital is fully detailed by Erasmus Wilson in his "History of The Middlesex Hospital," published in 1845. For subsequent facts I am greatly indebted to Mr. W. T. Hillier, who has diligently searched the Hospital Minute Books for this purpose. It may be of interest to append here a few extracts, in addition to those utilized in the foregoing pages:—

Special General Court, 27 Jan. 1842.—Amended Rules and Regulations of the Cancer Establishment:—

(1) That a ward be always kept open for the admission of at least ten Female Patients afflicted with Cancer.

(2) That in consideration of the benefaction of Mrs. Stafford three beds be reserved in the ward called after her name for Male Patients afflicted with Cancer.

(3) That In-patients should be persons afflicted with Cancer (including every variety of malignant disease) requiring operation; also those with the disease in an acute stage, *i.e.*, spreading rapidly, attended with great suffering, or persons afflicted with these diseases returning after operation, "such cases to remain in Hospital until relieved by art or released by death;" but that no person should be entitled to so remain until after an interval of at least two months from admission, and then only on the certificate of the surgeon in attendance.

(4) That patients afflicted with Cancer (including every variety of malignant disease) should, as Out-patients, be relieved with advice and medicine for an unlimited period, and that cases of this description be admitted as In-patients on the recommendation of the surgeons for a limited period, not to exceed two months without the special permission of the Weekly Board of Governors.

(5) That, in conformity with the wishes of the original Founder of this Establishment, a Book be provided wherein the surgeons shall enter respectively the names of their patients, together with a general statement of their cases, and such other information as may be from time to time required by the Weekly Board, and should any extraordinary circumstance occur in the progress of a case, or should any remedy be providentially discovered, a record should be made thereof and published for the benefit of society.

(6) That all benefactions to this Establishment be funded.

(7) That any surplus of interest be laid out in 3 per cent. Consol Annuities, but that it shall be allowable for the Weekly Board to employ such surplus in sending such patients as come within the Rules of the Cancer Establishment to the seaside.

(8) That in regulating the accounts of the Cancer Establishment, In-patient's expense be reckoned at £40, Out-patient's £1.

Weekly Board, 1 Feb. 1842.—Ordered that a gratuity of £2 2*s*. be given to the Night Nurse of the Cancer Ward for her attention in extinguishing the gas lights of the Hospital at daybreak during the last two years.

Weekly Board, 25 April 1843.—That patients in the Cancer Wards shall be allowed 2 ozs. of tea and 1 lb. of sugar per week, half those quantities having been the previous allowance.

Weekly Board, 30 March 1847.—Ordered that a gratuity of £20 be given to the Matron, £5 5*s*. to the Cook, and £1 1*s*. to the Night Nurse of the Cancer Ward for their services during the past year.

Special General Court, 1 Jan. 1849, H.R.H. the Duke of Cambridge in the Chair.—"That a small ward of four beds for Male Cancer Patients be annexed to Whitbread's Ward, which is occupied exclusively by female patients, thereby carrying out to the fullest extent the benevolent intentions of the founder of that ward."

Weekly Board, 20 Jan. 1852.—The Secretary reported that the Medical Committee, having considered the question referred to them by the House Committee whether any more suitable article than feathers could be adopted for the beds of the patients in the Cancer Wards, were of opinion that the Spiral Spring Bedstead might be tried, especially as that could be done without any expense, as there were some already in the Hospital.

Weekly Board, 19 April 1853.—Resolved to apply to next Quarterly Court for authority to appropriate a sum not exceeding £1400 in the purchase and fitting up of a Leasehold House in Norfolk Street, in order to augment the accommodation of the Cancer Department of the Hospital, upon the receipt of funds arising out of the bequest of Sir Joseph de Courcy Laffan for the Cancer Wards.

Weekly Board, 28 June 1853.—Special report read proposing alterations of upper floor of Hospital to afford accommodation for increased number of Cancer Patients.

Weekly Board, 11 Jan. 1859.—The report of the Medical Committee of the 1st instant was read, recommending that in reference to the Rev. Hugh Reed's application to be allowed to try a remedy he had for Cancer, he be informed of the rule of the Hospital that, as a preliminary measure, he must disclose to the Physician or Surgeon,

under whose immediate care the patient was upon whom the experiment was proposed to be made, the nature of the remedies to be applied.

Weekly Board, 5 March 1861.—Resolved to adopt the suggestion of the Medical Committee for the establishment of a separate Out-patient Department for the attendance upon Cancer Patients exclusively, who shall be seen upon one or more days in the week, either with or without letters from Governors or Subscribers. Resolved, that in addition to the admission of Cancer Patients into the Cancer Wards upon the recommendation of Governors or Subscribers, the Surgeons be authorized to admit other proper cases without such letters of recommendation, subject to the following regulation, that, if admitted without any letter of recommendation from a Governor or Subscriber, such cases shall be reported on specially to the next Weekly Meeting, and that the admission be regarded as specially subject to consideration and approval by the Board.

Weekly Board, 12 March 1861.—The Visiting Governors report that of the twenty-six beds in the Cancer Wards twenty were occupied, eighteen by cancer patients and two by surgical cases.

Weekly Board, 26 March 1861.—Resolved that the Scheme proposed by the Medical Committee for the establishment of a separate and free Out-Patient Cancer Department be approved and recommended for adoption by the next General Court of Governors. (In the Scheme it was proposed that "such patients should be attended by the Senior Assistant-Surgeon, Mr. Nunn, exclusively, on different days and in another room to those devoted to the general surgical out-patients.")

Weekly Board, 28 April 1868.—Reported that there are now thirty-two beds in the wards specially appropriated to Cancer Patients.

Weekly Board, 14 May 1878.—Dr. Greenhow's offer and suggestion for the opening of a Male Cancer Ward, by acquiring two houses adjoining the Hospital in Cleveland Street, considered.

Weekly Board.—In 1885 many discussions took place upon the subject of a special Male Cancer Ward. The Board eventually suggest the conversion of "Handel" Ward.

Weekly Board, 2 November 1886.—Recommend Quarterly Court to increase number of endowed Male Cancer Beds from six to eight, to devote "Handel" Ward to them, and to rename it "Greenhow."

Weekly Board, 9 February 1896.—Tender for demolition of houses in Nassau Street accepted. The Scheme for dealing with the site not yet considered.

Weekly Board, 31 March 1896.—Plans for New Cancer Wing approved.

Weekly Board, 7 February 1899.—The Chairman having made a statement, as a preliminary, in view of the opening of the New Wing for Female Cancer Patients, and more particularly in regard to its medical supervision for carrying out the wishes of the original founders of the Cancer Wards, it was, after some discussion, moved by Sir Arthur Watson, seconded by the Hon. Spencer Lyttleton, and resolved unanimously:—

"That the Weekly Board of Governors are of opinion that, in the arrangements to be made for the medical supervision of the new Female Cancer Wards, endeavours should be made to give effect to the wishes of the original founders, which are expressed in the conditions submitted by the late Samuel Whitbread, Esq., in 1791, in the following terms, viz.: 'The relief of persons affected with Cancer, and the investigation of a complaint which, though extremely common, is, both with regard to its natural history and cure, but imperfectly known;' and likewise laid down in the will of the late Mrs. Alithea Maria Stafford, as follows, viz.: 'Curing persons affected with Cancer, and of investigating and promoting our general knowledge of treating that dreadful disorder.' And the Board would be glad if the Medical Committee would consider how this could best be done. The enhanced facilities for pathological and bacteriological study in the Hospital is, they consider, an additional reason why some practical steps should be taken in this direction."

THE PATHOGENIC ACTION

OF

BLASTOMYCETES.

By HENRY W. P. YOUNG, M.D.

I.

The study of the Blastomycetes has of recent years received considerable attention, chiefly owing to the work of San Felice and the theories which he has enunciated as to the part played by them in the causation of malignant tumours.

Their pathogenic action seems to have been first studied by Claude Bernard,* who in 1847 made intravenous injections into animals of ordinary brewers' yeast suspended in water. When yeast only was injected no results were produced; but when simultaneously a solution of sugar was introduced into another vein, or into the subcutaneous tissue, the first symptoms were similar to those obtained by injecting alcohol, and were followed by acute gastro-intestinal catarrh and death. Rabbits died in about twenty-four hours, while dogs succumbed in three days.

Grohe† in 1870 inoculated animals with beer-yeast into the veins and into the peritoneal cavity, and obtained whitish nodules in the lungs, heart muscle, liver, and kidneys.

* Claude Bernard, "Expériences sur les manifestations chimiques diverses des substances introduites dans l'organisme" ("Archives générales de médicine, 1848," vol. xvi., p. 82).

† Grohe, "Berliner Klinische Wochenschrift," Januar 3, 1870, s. 9.

Popoff,* making use of the same material, found that small doses introduced into the blood-vessels, stomach, pleural cavity, or subcutaneous tissue, produced only slight rise of temperature, which subsided after two or three days; but when larger doses were employed an acute septic intoxication followed, with hæmorrhagic gastro-enteritis and death. He did not observe any nodules in the internal organs of the animals experimented with.

In 1886 Falk† found that no results were obtained—neither blood-poisoning, mycosis, nor intoxication—after injecting into the pleura, peritoneum, veins, or subcutaneous tissue, beer-yeast which had been purified.

None of these observers worked with pure cultures.

Neumayer‡ in 1891 carried out experiments with pure cultures of S. apiculatus: two cultures from beer, one alcoholic yeast, two torulæ, and three wild yeasts. He demonstrated that men and animals might be given regular doses of yeast without any ill effects, provided that all fermentable substances were excluded from the diet during the treatment; but if these were allowed, symptoms of gastro-intestinal disturbances were produced.

Inoculations of yeast into the subcutaneous tissue of mice and guinea-pigs were without results, except for slight inflammatory reaction at the site of inoculation. When injected into the veins of rabbits large quantities caused collapse and death, but small doses produced little or no effect.

Raum,§ in the same year, published his work on the morphology and physiology of the yeast plant. He also made use of pure cultures in his experiments.

Intravenous injections produced results in small animals which varied with the dose. If this were small a slight rise of temperature occurred, accompanied by some quickening of the respiration. Large doses, however, caused the rapid onset of severe dyspnœa with lowering of the temperature. Collapse usually followed and the animal succumbed.

* Popoff, "Berliner Klinische Wochenschrift," 1872, s. 518.

† Falk, "Ueber Hefe Einspritzung" ("Archiv. für Anatomie und Physiologie," 1886, band. xvii., supplement).

‡ Neumayer, "Archiv. für Hygiene," 1891, bd. xii., s. 1.

§ Raum, "Zur Morphologie und Biologie des Sprosspilze" ("Zeitschr. für Hygiene," bd. x., s. 1).

In one case which he examined after death, the blood-vessels of the lungs were found to be obstructed by thrombi in which yeast cells were present. There were no lesions in the liver or kidneys. In another animal the escape of the micro-organisms into the subcutaneous tissue caused a solid tumour at the site of inoculation. After three weeks the swelling was in a state of caseous degeneration, and in the broken-down tissue yeast cells could still be recognized.

The first member of the group of blastomycetes known to be pathogenic to man was Oidium albicans, discovered by Langenbeck in 1839, and later assigned to the saccharomycetes by Rees. Although the proper botanical position of this micro-organism still remains a matter of some doubt, its appearance on certain media in the form of round or oval cells which multiply by gemmation seems at any rate to justify one in including it among the Blastomycetes.

In addition to its usual *rôle* as a parasite of the mucous membrane of the mouth, S. albicans may produce a more general infection.

Payne,* in his "Manual of Pathology," refers to the case of an infant, in which, after death, the ileum was found covered with a growth of this parasite; and the same author quotes a case in which the blood being infected by it, death followed from embolism of the cerebral vessels.

Klemperer† in 1885 made experiments on animals with this organism, and obtained a general mycosis of all the organs. Death occurred in from twenty-four to forty-eight hours after inoculation.

Roux and Linossier‡ worked with this fungus, and described its morphological and biological characters. They also inoculated cultures of it into animals and obtained a general infection.

A case of pseudo-membranous angina in a syphilitic woman, due to the presence of S. albicans in its yeast form only, was described by Tessier.§ Intravenous injections into small animals

* Payne, "Manual of Pathology," 1888.

† Klemperer, "Ueber die Natur der Soorpilzes" ("Centralblatt für Klinische Medicine," 1885, s. 849).

‡ Roux and Linossier, "Archives de Méd. Exp.," 1890, tome ii.

§ Tessier, "Contributions a l'étude du champignon du Muquet" ("Archives de Méd. Exp.," 1893, tome v., p. 29).

of the parasite from this case produced a general mycosis with predominant lesions in the kidneys, liver and spleen; subcutaneous inoculations were followed by abscesses, and when introduced into the peritoneal cavity a seropurulent peritonitis ensued. Tessier always found the organism in its filamentous form in the tissues. He quotes a case recorded by Schmorl in which a general infection occurred.

Artault* found S. albicans in the contents of the cavities of the lungs of a phthisical patient.

An organism morphologically similar to this parasite, but differing from it in its pathogenic action, was isolated by Grasset† from an abscess of the gum. All inoculation experiments, both subcutaneous and intraperitoneal, produced suppuration with the formation of thick white caseous pus, in which the parasite was present in pure culture. When inoculated into the veins no results were obtained excepting suppuration in the track of the needle. The abscess after a time healed and the animals recovered.

A case of pseudo-membranous angina ascribed to a blastomyces is recorded by Troisier and Achalme.‡ It occurred in an enteric patient in whom the pharynx, tonsils, soft palate, and uvula were covered with a soft, white, slightly viscid membrane. The parasite was a yeast form without filaments, and differed from *S. albicans* in the characters of its growth or culture media. It formed spores on peptonized alkaline gelatine, and they regarded it, therefore, as a true saccharomyces.

Busse's§ case, of which the first report appeared in 1894, seems to be the first definite instance of genuine yeast infection occurring in a human being.

The patient was a woman, aged thirty-one years, with a good family history, but who had suffered from scrofula in her childhood. Shortly after parturition a localized painful thickening of the skin over the front of the left tibia was

* Artault, "Flore et fauna des Cavernes pulmonaire" ("Archives de Parasit.," Paris, 1898, tome i., No. 3).

† Grasset, "Étude d'un champignon pyogène parasite de l'homme" ("Arch. de Méd. Exp.," 1898, tome v., p. 665).

‡ Troisier et Achalme, "Archives de Méd. Exp.," 1893, v., p. 29.

§ Busse, "Ueber Saccharomycosis hominis" ("Archiv. von Virchow," Path. Anat. und Physiology). 1895. "Ueber parasitare Zelleinschlüsse und ihre Züchtung" ("Centralblatt für Bakt.," 1894, bd. xvi., s. 175).

noticed, which increased in area in spite of treatment. Not long after this first appeared, a painful swelling of the knee developed, with effusion into the joint. The swelling subsided after a few weeks. On examination about eight months after the onset of the disease, the affection of the skin over the tibia was found to have developed into a soft fluctuating swelling of which the diagnosis lay between a chronic abscess and a soft sarcoma. As the woman had wasted to a considerable degree, an operation was decided upon.

The tumour after removal was sent to Busse for examination, and the discovery of the presence of a parasite of the nature of a blastomyces was made.

During the patient's stay in the hospital, abscesses appeared on the face, and, breaking down, formed ulcers. The same parasite was obtained from the base of these sores. A painful area was then noticed on the skin over the right ulna. This softened and developed into a fluctuating swelling which, on being opened, was found to contain yellowish-brown pus in which were to be seen large giant cells and many blastomycetes, both free and included in the cells. A similar tumour developed over the left sixth rib in the mammary line. This last was not opened before death. The patient became profoundly emaciated and suffered great pain over the region of the ileo-cæcal valve and in the back of the neck. Finally, death from exhaustion occurred thirteen months after the first appearance of the disease.

At the autopsy lesions were observed in the liver, kidneys, and spleen, which microscopically were composed of granulation tissue with many giant cells in the more central portions. These cells contained one or more yeasts, and free parasites were also present in considerable numbers. In the apex of the right lung there was a firm nodule of the size of a hen's egg, containing calcareous matter. One or two smaller nodules were situated in the left lung. In the left axilla there was a large swelling with soft semi-fluctuating contents.

The primary tumour removed by operation was 6 cm. long, 4 cm. broad, and 2 cm. in thickness. It contained a central cavity filled with a brownish-red semi-fluid substance.

The microscopic appearance of the tumour to some extent resembled that of a giant-celled sarcoma. It was composed of

a granulation tissue very rich in small round cells, and contained a large number of giant cells with peripherally placed nuclei. In the outer layers of the growth fibrous tissue predominated.

The blastomycetes, which were very numerous, appeared both free in the tissues and included in the cells, especially in the giant cells. Cultures of the organism were obtained from all the lesions. It grew freely on all the ordinary laboratory media.

In dogs and rabbits, subcutaneous injection produced local abscesses which, after a time, discharged their contents and healed up, the animals recovering. Intraperitoneal injection was followed by slight fibrinous peritonitis and hyperplasia of the mesenteric glands. White mice, inoculated in the muscles of the back, died in from four to ten days with degenerative changes in the muscular fibres, the parasite being present in the blood.

In a second series of experiments performed somewhat later, the mice lived longer after injection, and in some instances larger or smaller white swellings were found at the site of inoculation containing semi-caseous material. Small white nodules were also present in the lungs, kidneys, and brain.

Gilchrist* in June 1894 reported to the American Dermatological Society a case of dermatitis in the lesions of which a yeast was present.

This case, which had been under the care of Dr. Duhring at Philadelphia, had been diagnosed clinically as a typical example of chronic scrofuloderma.

Gilchrist, to whom portions of the affected skin were submitted for examination, failed to find *Bacillus tuberculosis* in the tissues, but found instead certain bodies which he suspected of being vegetable cells.

Sections through the base of the lesion presented the following microscopic appearances :—

At the surface an irregular mass of detritus, consisting of epithelium and pus cells, fibrin, coagulated albumen, and red blood corpuscles. The stratum corneum was infiltrated with small collections of pus. In the rête mucosum the epithelium was enormously hypertrophied, and presented irregular pro

* Gilchrist, "A case of Blastomycetic Dermatitis in Man" (John Hopkins "Hospital Reports," vol. i., 1896).

longations extending downwards into the corium. The chief feature, however, was the occurrence of numerous well-defined miliary abscesses, the largest of which were just visible to the naked eye. They contained polynuclear leucocytes, nuclear detritus, peculiar nuclear cells, and occasional giant cells.

The corium also shewed considerable pathological changes. Miliary abscesses similar to those in the epidermis were present, but less numerous, and large collections of cells were to be seen, especially around the blood-vessels. The latter consisted of granulation cells of various sizes, polynuclear leucocytes, and occasional giant cells.

The parasites were always present in the abscesses, though in varying numbers, usually from four to six in each. None appeared on the surface of the skin, but a few were scattered throughout the corium. They were always surrounded by inflammatory material, and were never intracellular as regards the epithelial cells. They were occasionally included in the giant cells.

The general structure and size of these bodies, their reproduction by gemmation, and their reaction to caustic potash and acids, led Gilchrist to the opinion that this was a case of blastomycetic infection; but no cultures of the organism were made, and no inoculation experiments performed.

The first report of this case preceded that of Busse's by about two months.

A second case of blastomycetic skin infection, similar in many respects to the above, was described by Gilchrist and Stokes* in 1898.

The patient was a man, thirty-three years of age, in whom the disease began as a small papule on the skin just behind the left mastoid process. The papule soon became a pustule, which broke down into a small ulcer, and this began to spread very slowly in an anterior direction. In four years it had spread on to the cheek, the older portion having healed spontaneously.

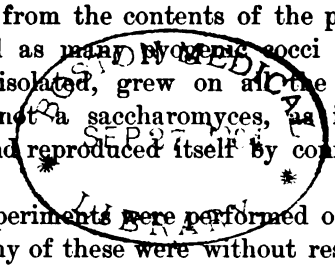
At the end of seven years the external canthus of the left eye was reached, and eventually the disease affected the eyelid and crossed the bridge of the nose on to the right cheek.

* Gilchrist and Stokes, "A case of Pseudo-Lupus Vulgaris caused by a Blastomyces" ("Journal of Exper. Med.," New York, 1898, vol. iii.).

Similar patches had in the meantime developed on the back of the hand and on the right side of the scrotum. This last healed up after having reached the size of a silver dollar.

The affected areas presented the appearance of lupus vulgaris, the surface being dry and scaly, with occasional pustules. There was a tendency to heal spontaneously in the older portions with the formation of thin scar tissue. Around the left eye, however, it was red and raw looking, and bled easily. On the back of the hand it had a more warty aspect.

Cultures made from the contents of the pustules contained yeast-cells as well as many pyogenic cocci and some bacilli. The first, when isolated, grew on all the usual laboratory media. It was not a saccharomyces, as it produced true mycelial forms, and reproduced itself by conidia as well as by gemmation.



Inoculation experiments were performed on mice, dogs, and guinea-pigs. Many of these were without results. Two dogs, in which a pure culture was injected into the jugular vein, developed a discharge from the nasal passages and became emaciated. When killed, at the end of two months, the lungs were found to be thickly studded with small yellowish-white nodules, which microscopically resembled in their structure the granulation produced by Bacillus tuberculosis. The micro-organism was present in large numbers, and was obtained in pure cultures. Some positive results were also obtained on inoculating guinea-pigs. The microscopical appearance of sections of the affected skin was practically identical with that of Gilchrist's first case.

In September 1895 Curtis* of Lille published an account of a growth which had been removed from the upper part of the right thigh of a young man, who also had a large abscess in the lumbar region.

The tumour, which had been growing for about three months, was soft and semi-fluctuating. It had developed in the subcutaneous tissue of Scarpa's triangle, the skin over it being unaffected. The growth was composed of a soft gelatinous tissue, and had the appearance of a sarcoma in a state of

* Curtis, "Note sur un parasite végétale" ("Presse Méd. Belge," Bruxelles, 1895, p. 370).

advanced mucoid degeneration. From both the tumour and the abscess a micro-organism was isolated, to which the name "Saccharomyces subcutaneas tumefaciens" was given.

Operative treatment on both lesions appeared successful, but the patient died ten months after with meningeal symptoms of an obscure nature. No autopsy was performed.

In a later paper Curtis* stated that the parasite was analogous to those yeasts described by Busse and San Felice, but was to be distinguished from them by certain differences. It grew best on acid and neutral media, fermented glucose, and converted saccharose into invert sugar. It was pathogenic for rats and mice, producing subcutaneous swellings analogous to those observed in the original case. In the tissues it occurred in encapsuled and non-encapsuled forms.

The researches of San Felice,† set forth in a series of papers which began to appear in 1895, endowed the blastomycetes with an importance hitherto not ascribed to them.

This observer, working with a yeast which he had isolated from the surface of ripe fruit, and which he had named S. neoformans, carried out an enormous number of inoculation experiments on various kinds of animals, including guinea-pigs, mice, rabbits, dogs, sheep, and chickens. The inoculations, performed in various ways, were followed by a general infection with the production of white nodules in the organs and in the subcutaneous tissue.

Adopting new methods of staining, San Felice investigated very thoroughly the microscopic appearance of the organism in the tissues, and succeeded in convincing himself of the identity of the yeast-cells with the so-called cancer bodies. Finally, he formulated the doctrine that malignant tumours of men and animals are due to the action of parasites belonging to the blastomycetes. The tumours, however, which he obtained in animals were, with two exceptions, not of an epithelial nature, but typical granulomata.

* Curtis, "Contribution à l'étude de la Saccharomycose humaine" ("Annales de l'Institut Pasteur," 1896, vol. x., p. 448).

† San Felice, "Ueber die pathogene Wirkung der Sprosspilze" ("Centralblatt für Bakt.," 1893, s. 625). "Ueber eine für Thiere pathogene Sprosspilzart" (*Ibid.*, 1895, s. 113). "Ueber eine neuen pathogenen Blastomyceten" (*Ibid.*, 1895, s. 521). "Ueber die pathogene Wirkung der Blastomyceten" ("Zeitschrift f. Hygiene," 1896, xxi., 32; xxii., s. 171; xxiv., s. 463).

These two exceptions occurred in dogs, and were regarded by the author as positive proof of his theory.

The first case followed the injection of a pure culture of S. neoformans into each of the most posterior pair of mammary glands. An initial inflammatory reaction occurred which soon subsided; but after a month a slight swelling of the gland was noticed which gradually increased. An enlargement of the inguinal glands was also observed. The animal, which had become greatly emaciated, was killed at the end of ten months.

Post-mortem the mammary gland contained a new growth which presented macroscopically and microscopically the appearance of a glandular carcinoma, and metastases of a similar character were present in the inguinal glands. The internal organs were unaffected.

Blastomycetes were demonstrated by staining methods in the peripheral portions of the tumour and in the glands. In the older portions of the swelling they were absent. The majority of the parasites were free, but many were included in the epithelial cells. All attempts to obtain cultures of the organism failed.

The second positive case was obtained by inoculating S. neoformans into the testicles of a dog. A similar initial inflammatory reaction occurred, and shortly after that subsided. The testicles began to enlarge, and a puriform discharge, in which yeasts could be seen under the microscope, appeared from the urethra. The animal died suddenly at the end of five months for some unknown reason. After death San Felice found new growth in the testicles, many hard nodules between the penis and the skin over it, and a conical growth on the glans.

The neoplasm proved to be of the nature of a glandular carcinoma, and contained yeast forms both free and included.

No cultures could be obtained either from the growths or from the urethral discharge.

Roncali* found a yeast in what he described as an adeno-carcinoma of the ovary of a woman, who died twelve days after

* Roncali, "Sopra particolari parassiti rinvenuti in un adeno-carcinoma. Il Policlinico." Translation, "Die Blastomyceten in den Adeno-carcinomen des Ovariums" ("Ctblt. für Backt.," xviii., s. 353).

the operation for removal of the growth, with symptoms of acute nephritis. Metastases were found after death in the liver, kidney, and great omentum. The organism stained well in the tissues with San Felice's methods, but no cultures were obtained.

By the same staining methods Roncali* claims to have demonstrated the presence of yeast forms in five cases of sarcoma. Here again the parasite was not isolated.

Since then Roncali has obtained cultures of an organism which he named *S. vitrisimile degenerans*, from three cases of malignant tumours out of thirty-eight which he examined.

The cases from which cultures were obtained were: firstly, an epithelioma of the tongue with metastases in the axillary glands; secondly, a sarcoma of the breast; and thirdly, a primary adeno-sarcoma of the transverse colon which had spread to the great omentum and mesentery.

The macroscopical and microscopical appearances of the growth in the last case, as described by Roncali, resemble in many ways that of the swellings which I obtained in my inoculation experiments hereafter described, especially in the very large numbers in which the parasites were present. Epithelial proliferation and many giant cells were, however, observed in this tumour. Both Roncali and Plimmer are firm believers in San Felice's theory.

Plimmer† examined 1,278 cases of cancer; and, by his own special methods of hardening and staining, demonstrated the cancer "parasite" in 1,130. Of the unsuccessful cases, ninety were fibrous or degenerated. The parasite, according to Plimmer, is not found in all parts of the cancer, being present at the growing edge and not in the degenerated parts or "when fibrous tissue is destroying or digesting the cancer cells." "They may be seen free in an alveolus, still surrounded with their capsule, and having the same reaction which they have in

* Roncali, "Die Blastomyceten in den Sarkomen" ("Centralblatt für Bakt.," xviii., s. 432). "Di un nuova blastomicete isolato da un epitelioma della lingua e della metastasi ascellari di un sarcoma della ghiandula mammaria" (*Ibid.*, xx., 481, 1896). "Mikrobiologische Untersuchungen über einer tumour des Abdomens" (*Ibid.*, xxi., 517). "Klinische Beobactungen über einen Fall von primaren Adeno-carcinom" (*Ibid.*, xxiv., 361, 1898).

† Plimmer, "The Practitioner," April 1899, vol. xxii., p. 430.

the cells." He denies that the cancer bodies are the result of degeneration, alleging that "they have none of the reactions of any known degeneration, and are not to be found at all in the parts of a cancer which are degenerating, but only in the actively growing parts; that they are not found in any other tissue save only sarcoma; and that they can and do multiply in cancer tissue kept outside the body, and can be grown on culture media."

Plimmer isolated an organism of yeast form from a breast cancer of two months' duration, and grew it on an infusion of cancer tissue. Inoculated into the peritoneal cavity of guinea-pigs, it produced small transparent nodules on the peritoneum and in the liver, spleen, omentum, intestines, and lungs. Microscopically the growths consisted of round cells, and contained numbers of the parasites which were, for the most part, included in the cells.

Since the publication of Gilchrist and Stokes' paper four other cases of Blastomycetes Dermatitis have been recorded in American literature, namely, cases reported by Gideon Welles, Hessler, and Hyde and Hektoen.

Gideon Welles'* case began as a small pimple on the back of the first phalanx of the left little finger of a man aged twenty-nine, and gradually spread until the greater part of the back of the hand was involved. The affected area presented a raised, fungating mass of a dark cherry red colour, sprinkled with small pustules. The disease had lasted for eleven years. Secondary infection had occurred in several places, and these alone had healed under the treatment.

It was diagnosed as chronic tuberculosis disease of the skin; but on a search for the Bacillus tuberculosis being instituted, none were to be found, blastomycetes being seen instead. Histologically it was identical with Gilchrist's case. No cultures of the organism were obtained.

Hessler's† case occurred in a healthy man who was infected in the skin of the face by a barber's razor. A red papule developed which afterwards suppurated. A budding organism,

* Gideon Welles, "A case of Blastomycetic Dermatitis" ("New York Medical Journal," March 1898, p. 427).

† Hessler, "Blastomycetic Dermatitis" ("Indiana Med. Journal," Aug. 1898).

somewhat smaller than those isolated by other observers and oval in shape, was isolated from the lesion.

The Hyde-Hektoen* case began as a small reddish spot on the right leg, and extended gradually so as to cover the whole of the anterior surface of the limb from the knee to a little above the ankle, "presenting a tender, painful, and hæmorrhagic sore somewhat resembling an ulcer." Eventually the sore healed under treatment except over a very small area.

Three years after the first onset of the disease on the leg a similar affection appeared on the left thumb, and gradually involved the dorsal surface of the left hand and wrist and lower portion of the left arm.

"The sore was dull reddish in hue, sharply defined in outline, and had a peculiar bluish-red border extending about four millimetres away from the edge of the affected area. The body of the patch was made up of an elevated mass of infiltration, with a verruciform development of fine, pin-head sized papillæ, projected externally and moistened with a glutinous secretion."

Parasites of the nature of blastomycetes were demonstrated in the tissues and obtained in cultures.

This case was remarkable for the rapidity with which the disease healed, and the patient improved during the administration of potassium iodide.

The organism produced local abscesses when injected subcutaneously into white rats, guinea-pigs, and rabbits, occasionally followed by death after two to four weeks. Intraperitoneal and sometimes subcutaneous injection led to the development of disseminated greyish nodules in the lungs and liver.

Hyde and Hektoen also quote a case which had been under the care of Prof. Murphy and Dr. Coates. The patient was a married woman aged sixty-four, in whom a circular, elevated cauliflower-like mass, the size of a penny, with an irregularly ulcerated red surface, had developed on the posterior surface of the lower third of the right leg. The growth was regarded as malignant and was removed by a circular incision. Subsequent microscopical examination, however, revealed marked proliferation of the epithelial elements and numerous miliary abscesses which contained organisms resembling yeasts. No cultures were made from the growth.

* Hyde and Hektoen, "A contribution to the study of Blastomycetic Dermatitis" ("British Journal of Dermatology," July 1899, vol. xi., No. 7).

Maffucci and Sirleo* made cultivations from thirty-nine tumours, including twenty-seven cancerous growths and eleven sarcomata, many of which had suppurated. They obtained cultures of various yeasts from seven of them; but in only two instances were the micro-organisms pathogenic for small animals.

Portions of the growths were also examined microscopically. Yeast cells were observed in the tissues of only three of the above-mentioned seven cases, and in two others. During their investigations the air of the laboratory was examined for the presence of blastomycetes. Two different varieties were found to be present, and these appeared to be identical with some of those obtained from the tumours, but did not account for them all.

The same authorities have reported two cases of accidental blastomycetic infection occurring in guinea-pigs. The organisms obtained from these animals caused a general infection with the production of granulomata when experimentally inoculated.

Maffucci and Sirleo, as the result of their investigations, thought that many malignant tumours were of infective origin; but though they did not absolutely deny that the blastomycetes could produce carcinomata and sarcomata, they considered that, as yet, there was no experimental proof.

From a malignant tumour of the mesentery Corselli and Frisco† isolated a yeast which in guinea-pigs caused death in from twenty-five to thirty days with great emaciation. In the peritoneum nodules were found whose constitution histologically resembled human sarcomata.

Bonome‡ studied twenty-three cases of malignant growths, and on microscopic examination observed yeast forms in six carcinomata and one sarcoma. He concluded that these parasites enter the tumours after they have developed, and that they

* Maffucci und Sirleo, "Weitere experimentelle Untersuchungen ueber einen pathogene Blastomyceten" ("Centralblatt für Allgemeine Path. und Path. Anatomie," 1896, bd. vii., s. 977).

† Corselli e Frisco, "Contributo alla etiologie de' tumori maligni annali d'Igiene sperimente," 1895. "Path. Blastomyceten beim menschen" ("Cblt. f. Bakt.," bd. xviii., 1895).

‡ Bonome, "Sull' importanza dei blastomiceti nei tumori" ("Atti del R. Istituto venuto di Scienze, Lettere ed Arti," 1898, t. ix.).

produce softening of the growths through rapid degeneration of their elements. Fifty-three cancerous growths were examined microscopically by Bianaghi,* who stated that he found bodies resembling blastomycetes in forty of them.

Monserrat† obtained cultures of blastomycetes by inseminating on glucose agar scrapings from the growing edge of carcinomata of the breast and uterus, all precaution being taken to avoid contamination with extraneous organisms.

A yeast which he obtained in this way produced nodules on the peritoneum and viscera when inoculated into the peritoneal cavity of small animals. These nodules were composed of epithelial cells, but in no case did he observe "an alveolar arrangement of the cells or any appearance resembling endotheliomata." The organism occurred both in the cells and free in the tissues. In some of the yeast obtained from the tissues spore formation was observed.

Léopold‡ examined malignant tumours for yeasts, taking the utmost precaution to obviate any accidental infection from the air. All cases in which ulceration had occurred were excluded. In pieces of fresh cancer tissue suspended in a hanging drop preparation upon a warm stage he saw, in nearly every case, "brilliant elements round or biscuit shaped," which he concluded were blastomycetes.

After many unsuccessful attempts he claims to have succeeded in isolating pure cultures of blastomycetes from four cases of cancer, namely, one case of carcinoma of the mammary gland, one of the uterus, and two of ovarian disease.

A small piece of cancer tissue was introduced into the peritoneal cavity of a rabbit. The animal died at the end of four days, and after death the liver and lungs were found to contain nodules of various sizes, presenting the appearance microscopically of a new formation of epithelial elements. Many yeast forms were observed in these nodules.

Léopold is convinced that the blastomycetes may be the cause of malignant tumours in man.

* Bianaghi, "Il Policlinico," 1898. "Zeitschrift f. Hygiene," 1895.

† Monserrat, "Observations on the Morphology of the Blastomycetes found in Carcinomata" ("Proceedings of the Royal Society," 1900, vol. lxvi.).

‡ Léopold, "Annales de Gynecologie et d'Obstetrique," Sept. and Oct. 1900, p. 333.

Aievoli,* Kahane,† San Felice, Roswell Park,‡ Pianese, and Wlaeff§ also claim to have obtained cultures of yeasts from malignant growths.

In human beings blastomycetes have been obtained from disease of a nature different from those already mentioned.

From a case diagnosed as chronic cervical endometritis in a young married woman, Colpe‖ isolated a parasite of this nature, which he thought was probably the cause of the affection.

The disease, which had resisted the usual antiseptic treatment, rapidly improved under the administration of vaginal douches of weak solutions of lactic and salicylic acids.

The organism produced no effect when inoculated in the ordinary way into rabbits, but a vaginal discharge lasting for fourteen days followed its injection into the os uteri.

Bossi¶ also found a yeast in the vaginal secretion in a case of endometritis, and Rossi Doria** claims to have demonstrated the presence of a similar parasite in a Deciduoma Malignum.

De Simone†† states that he found blastomycetes in sections of twenty hypertrophied tonsils which had been removed from boys and girls, but did not obtain cultures of the organism.

Foulerton‡‡ isolated a yeast from the urine obtained with a sterilized catheter from a case of chronic albuminuria.

From the urine of a patient De Gaetano§§ obtained a

* Aievoli, "Recherche sui Blastomiceti nei neoplasmi" ("Centralblatt für Bakt.," xx., 745).

† Kahane, "Présence d'une levure dans les cancers" ("La Sémaine Med.," 20 Mars, 1895).

‡ Roswell Park, "Philadelphia Med. Journ.," June 1900.

§ Wlaeff, "Levures pures dans un sarcoma d'uterus chez une femme" ("Compt. Rendus de la Société de Biologie," 1900, tome lii.).

‖ Colpe, "Hefezellen als Krankheitserreger im weiblichen genital canal" ("Arch. f. Gynäk.," 1894, bd. xlvii., s. 635).

¶ Bossi, "Atti del III., Congresso della Societe Italiano di ostetricia e ginecologia."

** Rossi Doria, "Blastomicete nel Sarcoma puerperala infettante (Deciduoma maligna)" ("Il Policlinico," 1896, iii., p. 91).

†† De Simone, "Ueber das Vorkommen von Blastomyceten in der hypertrophischen tonsille" ("Ctblt. f. Bakt.," xxii., s. 120).

‡‡ Foulerton, "On the Pathogenic action of Blastomycetes" ("Journ. of Pathology," 1900).

§§ De Gaetano, "Di un blastomicete pathogeno, dotato di rapido potere setticemico per la cavie" ("La Riforma Medica," 1897, vol. iii., p. 591).

similar organism which killed mice and guinea-pigs with great rapidity.

Busse* claims to have observed yeast cells in nasal polypi which he examined. He obtained cultivations in three cases, but did not feel sure that they were not an accidental contamination.

The same authority found blastomycetes in sections of a tumour growing from the cervix uteri of a child, and obtained the organism in pure culture. Inoculated into dogs and rabbits the yeast produced no results, but was toxic for mice.

Other observers have found similar parasites in animals. Thus Tokishige† in 1893 described an infectious disease which occurs in horses and cattle in Japan. This he proved to be due to infection by a yeast parasite.

The disease is characterized by the formation of hard, painless, circumscribed nodules in the subcutaneous tissue and, more rarely, in the mucous membrane of the nose. These swellings soften at the centre and form a thick glutinous or sanguineous pus. The affection spreads by the lymphatics, and, when the nasal mucous membrane is the seat of the affection, the trachea and bronchi are liable to become implicated. The disease is very chronic and may last several months, usually ending in death from cachexia and exhaustion.

A budding organism, to which he gave the name *S. farcimi-nosus*, was found in the nodules and lymphatic glands and in the discharges. Pure cultures were isolated and, when injected under the skin of horses, produced localized abscesses.

A similar disease occurring in horses in the south of Europe had been described by Rivolta‡ in 1873, who found in the lesions a parasite which he called *Crypto-coccus farciminosus*.

Fermi and Aruch,§ as the result of their investigations of the same affections, came to the conclusion that the organism was in reality a blastomyces.

* Busse, "Die Hefen als Krankheitserreger." Berlin, 1897.

† Tokishige, "Ueber pathogene Blastomyceten" ("Centralblatt für Bakt. und Parasitenk," 1896, bd. xix., p. 105).

‡ Rivolta, "Parassite vegetali," 1873, pp. 246, 525.

§ Fermi ü Aruch, "Ueber einer neuer pathogene Hefeart." ("Centralblatt für Bakt.," bd. xvii., s. 593).

Foulerton* recorded an apparently similar disease occurring in England in a cow, in the lesions of which he recognized bodies resembling yeast cells as they appear in the tissues.

San Felice† obtained a yeast which he called *S. lithogenes* from the glands of an ox. The animal had died as the result of a primary carcinoma of the liver which had spread to the lymphatic system. Calcareous matter was present in the tissues in the neighbourhood of the parasites. In guinea-pigs *S. lithogenes* caused death in about two months when introduced into the subcutaneous tissue. It produced a tumour at the site of inoculation and small nodules in the various organs. Calcareous masses occurred in the affected tissues, and were attributed to a degeneration of the yeast cells themselves. Mice died in eight days with a general infection, and in two sheep small nodules developed at the site of inoculation, which suppurated, the pus containing the parasite and calcareous matter.

Gotti and Brazzola‡ record a case of a mare which suffered from a mucoid discharge from the left nostril, in which a yeast, specially pathogenic to guinea-pigs, was discovered. The animal was killed and a gelatinous tumour found in the upper part of the left nasal cavity, involving the ethmoidal cells.

Memmo§ states that after many unsuccessful attempts he succeeded in isolating a blastomyces in pure culture from the brain of a rabbit, which had succumbed as the result of experimentally produced rabies. About the same time a similar parasite was obtained from the brain of a child which had died from hydrophobia.

In four other rabbits the same results were obtained.

Cultures of the micro-organism inoculated into guinea-pigs caused paresis of the hind limbs and, later, clonic spasm of the

* Foulerton, "On the Pathology of some Infective granulomata in Horses and Cattle" ("Journ. comp. Path. and Therapeutics," Edin. and London, 1898, vol. xi., p. 2).

† San Felice, "Ueber die Pathogene Werkung der Blastomyceten II." ("Abhandlung, Zeitschrift f. Hygiene," 1895, xxi., 894).

‡ Gotti e Brazzola, "Sopra un caso di blastomicose nasala in una cavalla" ("Memoria della R. Accod. della Scienze dell' Istituto di Bologna," 1897, ser. v., t. 6).

§ Memmo, "Beitrage zur Aetiologie der Rabies" ("Centralblatt f. Bakt.," 1896, bd. xx., s. 207).

limbs and death. Dogs also succumbed in from thirty to sixty days with some of the symptoms of rabies.

No macroscopic lesions were found in any of the animals after death. These results have not been confirmed.

The virulence of the commoner forms of the yeast family have been tested in recent years by Rabinowitsch, Foulerton, and others.

Rabinowitsch* performed inoculation experiments with fifty different kinds of blastomycetes. Of these only seven proved pathogenic to mice and rabbits, and all were harmless to guinea-pigs. No tumours were obtained in any of the animals. The author did not think that these seven species were identical with those described by other observers.

Foulerton,† however, obtained tumours at the site of inoculation, and occasionally nodules in internal organs in rabbits, with several of the yeasts he experimented with. These included one of the *S. cerevisiæ*, *S. pastoriani* I. and II., *S. albus*, *S. albus liquefaciens*, *S. ellipsoideus*, and *S. albicans*. All the animals died within a month of inoculation. Experiments on guinea-pigs were unsuccessful.

Foulerton isolated a yeast from two cases of pharyngitis, in one associated with the Klebs-Löffler bacillus. This yeast killed rabbits in from three to fifteen days, with the formation of soft white tumours at the site of inoculation and occasional metastases in the organs. Two guinea-pigs also gave positive results, and mice succumbed within forty-eight hours. To this organism he gave the name *S. tumefaciens albus*.

Experiments to discover the fate of the non-pathogenic varieties when injected into animals have been performed by Jona‡ and Gilkinet.§

The former used *S. apiculatus*, which was non-pathogenic for rabbits. When injected into the vascular system he found that it was killed by the blood and dissolved therein, never reaching

* Rabinowitsch, "Untersuchungen ueber pathogene Hefearten" ("Zeitschr. f. Hyg.," 1895, bd. xxi.).

† Foulerton, "On the Pathogenic action of Blastomycetes" ("Journ. of Pathology," 1900).

‡ Jona, "Die Schützmittel des organismus gegen die Blastomyceten" ("Centralblatt f. Bakt.," 1897, bd. xxi., s. 147).

§ Gilkinet, "Recherches sur la sort des levures dans l'organisme" ("Arch. de Méd. Exper. et d'Anat. Path.," tome ix.).

the organs of the body. In the same way when introduced into the peritoneal cavity it was destroyed there and did not pass into the blood or lymphatics. Results of a similar nature were obtained by subcutaneous injection.

Gilkinet,* who used one of the *S. cerevisiæ*, formed very similar conclusions. He attributed the destructive action to the tissue juices, the leucocytes taking no part.

Wlaeff,† by inoculating increasing doses of cultures of the yeasts of Curtis, Plimmer, and San Felice into geese and asses, found that he could render the animals immune against the organism. From the immunized animals he obtained a serum, which, he claims, possesses antitoxic properties. When injected into human beings suffering from cancer it is said to produce an inflammatory reaction at the site of inoculation and in the neighbouring lymphatic glands, and also a reaction in the malignant tumour. At first the cancer was slightly swollen; but after a time it diminished sensibly in volume, and after repeated injections became encapsuled. During the treatment the patient improved considerably. Pain and sleeplessness disappeared, the appetite returned, and the weight increased or at least remained stationary.

He has treated altogether forty patients in this way.

Wlaeff was able to produce immunity to blastomycetic infection in some of the animals experimented on by administering regular doses of the serum. He also found that when simultaneous inoculations were made with the serum and a pathogenic yeast the animals lived longer, and that in the tissues a well-marked inflammatory reaction developed around the parasites. In certain rats subjected to this treatment, followed by occasional additional doses of the antiblastomycetic serum, life was much prolonged, and the morbid process rendered so slow that it reached the epithelium of the intestines, biliary canals, and pancreas. Owing, as Wlaeff thinks, to the reaction provoked by the serum, the cells were no longer indifferent, but commenced to proliferate, producing thereby typical adenomatous tumours.

* Gilkinet, "Recherches sur la sort des levures dans l'organisme" ("Arch. de Méd. Exper. et d'Anat. Path.," tome ix.).

† Wlaeff, "Les blastomycetes dans la pathologie humaine" ("La Presse Méd.," 30 Mars 1901).

With the view of studying the nature of pathogenic blastomycetes and the pathological conditions which they produce in animals, I procured six of the already known members of this group, namely, *S. neoformans*, *S. lithogenes*, and a yeast isolated from an adeno-carcinoma of the ovary by San Felice (to whom I am indebted for permission to make use of these three cultures). I also worked with *S. tumefaciens albus* obtained by Foulerton from two cases of pharyngitis, and a yeast isolated from milk, kindly lent to me by Dr. Klein (who gave an account of it in a paper read to the Pathological Society of London in February, 1901); and lastly, I used two cultures of *S. albicans* obtained from the throat of two adult patients suffering from follicular tonsilitis.

In addition to these yeasts, I made use of one which I had myself isolated from milk, and which proved to be pathogenic for small animals.

As an example of a non-pathogenic blastomyces, a pure culture obtained from ordinary bakers' yeast was employed.

II.

Description of a New Yeast Pathogenic for Lower Animals.

This yeast, which I obtained from milk, when examined in hanging drop preparation appears usually as round, but sometimes as elliptical cells varying considerably in size. The smallest individuals are little larger than a large coccus, while some have a diameter equal to that of a red blood-cell, or even greater. In a culture about twenty-four hours old, young forms are seen which present the appearance of a dense circular mass of protoplasmic substance of a faintly greenish hue, in which little or no internal structure can be made out.

Somewhat older individuals possess a very definite enveloping membrane or capsule of clear refractile material, which appears bounded on the exterior by a well-defined dark line, and on the inner side by a somewhat fainter line. Usually in the centre

of the cell, but often eccentric, there is to be seen a space more or less circular in outline, which is much clearer than the rest of the protoplasmic contents. Outside the clear space a very highly refractile granule about the size of a staphylococcus appears; occasionally there is more than one of these.

A great many of the cells shew budding processes which, when recently formed, appear homogeneous, but many acquire an enveloping membrane before they separate from the parent. This enveloping membrane, at first, is continuous with that of the mother cell, but eventually septa pass inwards from the capsule at the point of constriction between them, shutting off the daughter cell from its parent. The cells may, however, still remain attached to one another. The stage at which the bud separates from the parent cell varies considerably. Separation may not take place until the new cell has acquired all the characters of the adult, or even undergone changes of degeneration. It is rare for a cell to produce a second bud before the first has left it; and chains of yeast cells are never seen in cultures. The buds are apt to take on abnormal forms, appearing sometimes as much elongated or roughly rod-shaped bodies, and are occasionally oval with the distal end pointed.

Well-marked Brownian movement is to be observed, and, even when suspended in a film of water which is absolutely at rest, there is a certain amount of very slow rotatory movement which can easily be detected in budding forms.

As the cell gets older, the clear space usually increases in size, and may occupy nearly the whole of the space within the enveloping membrane, the denser protoplasmic material being reduced to a crescent-shaped portion thrust to one side. This protoplasm may become filled with refractile granules.

When this yeast was cultivated on an unfavourable medium, as for instance on inspissated blood serum, the cells were found to have acquired a large size, and the denser protoplasm was collected into one or more spherical masses occupying the centre of the cell, the remainder of the contents of the capsule being quite clear and homogeneous.

When grown in broth the yeasts are rather smaller than when cultivated on solid media, and the new buds separate off earlier.

If a drop of a highly diluted aqueous solution of methyl

violet be placed at the edge of the cover slip of a hanging drop preparation, and be allowed to diffuse into the film of fluid in which the organism is suspended, the young cells are seen to quickly take up the dye and to stain almost homogeneously without revealing any special structure. In the older cells the denser protoplasm is the first to become coloured, but it does not stain evenly, being filled with irregularly disposed granular material which takes up the methyl violet much more than the remainder. The refractile granule remains colourless longer than the rest of the protoplasm, but eventually cannot be distinguished from the deeply-stained granular material. The clear space acquires a faintly violet hue.

The last portion to take up the dye is the enveloping membrane or capsule, but finally it stains deeply, obscuring effectually the structure of the cell.

In cover-glass preparations, dried and fixed in the ordinary way, the yeast cells stain very deeply with the aniline dyes, and retain the violet colouring in Gram's method against prolonged treatment with alcohol. They shrink a good deal in the process of preparing the film.

When the organism was grown under anærobic conditions for a fortnight or three weeks, many of the cells shewed marked degenerative changes. When stained by Gram's method the body of the altered cell remained clear and unstained or acquired a faint purple hue. Disposed in various ways within it were collections of irregularly-shaped, often discrete granules, which stained a dark purple. The capsule, if present at all, could not as a rule be distinguished from the remainder. In some cases the chromatic granules were absent, only a clear faintly-stained disc remaining. In others again the power of retaining the gentian violet at all was lost, and the cell acquired a pink colour from the eosin which was used as a counter stain. Many of these altered individuals were of very large size.

Very rarely one saw an abnormal form of budding, consisting of a tube-like outgrowth from the cell, rounded at the distal end, and about twice the length of the parent. In many respects these degenerative changes were identical with those observed in this and other yeasts when recovered from the tissues of an animal.

If a culture, which has been growing for three or four weeks on some solid medium such as potato, be examined in a cover-glass preparation stained with methyl violet or methylene blue, the yeasts are seen to be collected into large groups in which the cells are equidistant from one another and never in contact. Each cell is surrounded by six other cells, so that the appearance suggests the superficies of honeycomb, this effect being heightened by the fact that the circumference of each individual is slightly flattened opposite each of its neighbours, assuming in this way a more or less hexagonal form. To a certain extent, the older the culture the greater the distance between them, but it is never more than two-thirds of the diameter of the cells concerned. From each one may be seen one or more delicate strands or filaments passing to each of the six cells next to it.

In some parts of the preparations one may see individuals which possess a fairly definite halo of faintly-stained material, apparently similar to that of the connecting filaments. This appearance is probably produced by a material similar to that which composes the zooglœa of bacteria.

This yeast can be cultivated on all the ordinary laboratory media, except inspissated blood serum, and it grows best at a temperature approaching blood heat.

Growth is most exuberant on nutrient agar containing one per cent. of glucose. Here a greyish-white confluent streak appears in about twenty-four hours, possessing a moist and glistening appearance with regular margin and a smooth shining surface transversely convex.

It increases in amount for a week or so until a very rich streak, about one-third to half an inch broad, is obtained, the surface of which presents a longitudinal depression in the middle with a parallel ridge on either side of it. From this it slopes very gradually to the level of the medium. In the drop of fluid usually found at the bottom of the tube a thick white homogeneous growth appears. Little change occurs after it has reached this stage.

On maltose agar the organism grows much less freely, appearing as a moist-looking, opalescent streak raised above the surface of the medium and not presenting any median furrow. After a time a yellow tinge is acquired.

Glycerine agar produces a heavy, moist-looking, cream-coloured streak, which assumes a faintly brownish tinge after a week or two. On ordinary nutrient agar this yeast grows scantily.

On sterilized potato some thin confluent growth appears within twenty-four hours and rapidly increases in amount, becoming fairly copious in a day or two, with a surface raised slightly above the medium, and presenting little rounded elevations like those of granulation tissue. Eventually it becomes very moist and slimy-looking, and spreads a good deal over the medium as if it were a viscid liquid. This occurs chiefly on the lower part of the tube where the medium contains most water. At the upper end of the wedge of potato, where it is usually dried up, little white powdery masses develop. The colour of the growth is at first buff; but gradually becomes a rich, slightly-reddish brown.

On nutrient gelatin, minute, circular, white, discrete colonies are to be seen at the end of twenty-four hours. These increase in size until they reach that of a pin's head, usually remaining separate, but becoming confluent in some parts.

After the tubes had been kept about six weeks, a very slight amount of liquefaction of the gelatin immediately surrounding and underlying the colonies was observed.

No growth was observed on blood serum. In peptone beef-broth a white haze develops near the bottom of the tube, in which minute feathery particles are to be seen floating. A good deal of the growth, however, falls to the bottom and rests on the glass. The liquid is clear in the upper portions, but, if the tube be shaken, a general cloudiness is produced.

When one per cent. of maltose, glucose, or lactose is added to the broth the appearance of the growth is much the same, though it is rather more copious.

When cultivated on glucose agar and potato under anærobic conditions, no new colonies of this yeast developed.

To test for spore formation the yeast was placed on moist plaster-of-paris slabs and kept at room temperature for a fortnight. With Ziehl-Neelsen's staining method small round or oval bodies occurred in some of the cells, which retained the carbol fuchsin after treatment with one per cent. sulphuric acid for a minute and a half.

They occurred in varying numbers, from one up to six, and varied a good deal in size. The remainder of the cell stained very faintly with methylene blue, which was used as a counter-stain, without any indication of a capsule.

These bodies did not stain blue with Raum's method (in which warm methylene blue followed by cold bismark brown is used), as did the spores of bakers' yeast. I was not able to decide whether they were true spores or only refractile masses of protoplasm such as have been described. Such acid-fast bodies were not, however, present in the other pathogenic yeasts which I examined.

Inoculation Experiments.

Inoculation experiments with this yeast were performed on two white mice and four guinea-pigs. For mice ·5 c.c. of an emulsion in sterilized broth of a culture on maltose agar was used, and for guinea-pigs 1 c.c. was the dose.

TABLE OF INOCULATION EXPERIMENTS.

Animal.	Culture used.	Site of Inoculation.	Result.	Pathological changes produced.
Mouse No. 1.	Culture 4 days old.	Subcutaneous tissue of back.	Died in 35 days.	Large tumour at site of inoculation. Numerous small whitish nodules in great omentum. Small white patches in left kidney. Enlarged peribronchial lymphatic gland. Cultures of the yeast were obtained from the heart-blood, peritoneal fluid, and from all the lesions.
Mouse No. 2.	Same culture.	Peritoneum.	Died in 12 days.	Slight increase of fluid in the peritoneum. Some enlargement of the mesenteric glands. Pure cultures obtained from heart's blood and from peritoneal fluid.
Guinea-pig No. 1.	Same culture.	Muscles of thigh.	Killed at end of 9 weeks.	None. No cultures obtained.

Animal.	Culture used.	Site of Inoculation.	Result.	Pathological changes produced.
Guinea-pig No. 2.	Same culture.	Intra-peritoneal.	Died in 21 days.	Only slightly wasting. Enlargement of lymphatic glands in both groins, and also of pelvic and mesenteric glands. Some yellowish-white patches in the left kidney, no changes in liver or spleen. The examination was not made until end of 36 hours after death. Cultures of putrefactive organs only obtained. Yeast forms observed in smears or sections from lymphatic gland kidney and peritoneal fluid.
Guinea-pig No. 3.	Culture 10 days old from Mouse No. 2.	Muscles of thigh.	Killed at end of 6 weeks.	None.
Guinea-pig No. 4.	Same culture.	Intra-peritoneal.	Died at end of 6 weeks.	Appeared well nourished. Large gland in left groin. Great omentum infiltrated with nodular growth. Similar nodules in mesentery and parietal peritoneum. Some enteritis. Fæces contain blood. White nodules in intestinal wall. Spleen mottled. Mesenteric glands enlarged. Lungs swollen, pale, and waxy-looking. Peribronchial glands greatly enlarged. Pure cultures obtained from lungs, peritoneum, and heart-blood.

In mouse No. 1 a large tumour lay beneath the skin over the upper part of the back of the thorax and neck. This swelling was of irregular shape, presenting a main portion 1·5 c.m. long, by 1 c.m. wide and ·5 c.m. in thickness. From this a prolongation stretching on to the occipital region, while on the right side a chain of small nodules, about the size of hempseed, extended round to the submaxillary region. There was slightly increased amount of fluid in the peritoneal cavity. On the surface of the left kidney there were white patches; and nodules were seen in the cortex on section. In the anterior mediastinum was an enlarged gland the size of a sweet-pea seed.

Cultures from the heart blood, peritoneal fluid, kidney, and glands contained yeasts, but, owing to the fact that they were not made immediately after the death of the animal, other organisms were also present.

In sections, collections of the organisms were seen in the tumour and in the liver, spleen, kidney, and glands.

The second mouse succumbed on the twelfth day.

There was slight stickiness of the peritoneum and some slightly turbid fluid in the peritoneal cavity. The lymphatic glands in the mesentery were, to some extent, enlarged.

Pure cultures of the yeast were obtained from the blood in the heart and from the peritoneal fluid.

The organism was present in smears from the latter source.

Guinea-pig No. 2 died eighteen days after inoculation.

The upper part of the body, including the heart and lungs, were devoured by another animal kept in the same cage.

There was enlargement of the lymphatic glands in the groin and pelvis, and of the mesenteric glands.

The peritoneum appeared normal, but there was some increase of the peritoneal fluid.

In the left kidney some small yellowish-white patches were seen on the surface.

On section these patches extended about 1 millimetre's depth into the cortex. Other patches were observed deeper in this portion of the kidney, but none in the medullary tissue.

The right kidney, the spleen, and the liver appeared to be normal.

Cultures on glucose and maltose agar were made from the organs, but were much contaminated with putrefactive bacteria, and no yeasts could be obtained.

Smears from the peritoneum and lymphatic glands gave positive results, and in sections the micro-organism was seen in the spleen and kidney, and in the spinal cord.

The fourth guinea-pig died at the end of six weeks, and appeared to be in good health until within a few days of its death. The immediate cause of death was asphyxia. The body was not in the least emaciated, and fat was present in the subcutaneous tissue.

In the left groin there was a gland, the size of a filbert, of firm, pinkish-white material, slightly adherent to the surrounding tissues. On opening the abdomen a large mass of pinkish-white growth lay over the intestines in the middle line and to the right side, extending down into the right iliac fossa. This growth had developed in the great omentum which, near the stomach, presented numerous nodules of varying size, but, lower down, these were compressed together so as to form a more or less coherent mass from one-sixth to a third of an inch thick.

The material of which it was composed was gelatinous and semi-transparent, and was easily broken down by pressure.

Similar nodules, but of firmer consistence, were freely scattered over the mesentery and parietal peritoneum. The mucous membrane of both large and small intestines appeared inflamed, and blood was present in the fæces. Scattered very sparsely on the walls of the ileum, cæcum, and first part of the colon were small, firm, flattened nodules, roughly circular in outline, lying beneath the peritoneum, and projecting slightly into the lumen of the gut.

The largest was about the size of a split pea, convex in the external surface, and flattened and somewhat cup-shaped on the interior, the central area being depressed, and, in one instance, ulcerated.

The spleen was enlarged and of a pale brick-red colour, its surface studded with white circular nodules, and its substance filled with little white spherical nodules, the largest being equal to a hemp-seed in size. The whole organ in fact appeared to consist mainly of this newly-formed tissue.

A few similar nodules were seen in the liver and in both kidneys. The lymphatic glands in the pelvis and in the region of the aorta were greatly enlarged.

The lungs were much altered from the normal. They were obviously much swollen and firm to the touch, and presented a curious semi-transparent wax-like appearance. The surface, which was of a pinkish-grey colour, was here and there mottled with white patches produced by the presence of emphysema beneath the pleura.

On section the lung substance was composed of firm, granular, somewhat gelatinous material, mottled with branching

streaks of brownish pigment. All parts of the lungs were of the same nature. The organs floated in water. A large mass of firm growth encircled the bifurcation of the trachea, arising in the peribronchial glands.

The right side of the heart was distended with blood, while the left was empty. The brain and spinal cord were not examined.

Pure cultures of the organism were obtained from the heart-blood, lungs, peritoneum, and great omentum.

In smears prepared from the lymphatic glands, great omentum, kidneys, liver, spleen, lungs, and peribronchial glands, numerous parasites could be seen.

Sections of the lungs and of the omental tumour shewed them to contain enormous numbers of the organism, being almost entirely composed of yeast granulomatous tissue.

The first and third guinea-pigs were killed at the end of nine and six weeks respectively. They appeared to be perfectly healthy, and cultures from the organs were sterile.

III.

Experiments with Yeasts already described.

(1.) *S. neoformans.*

S. neoformans appears in hanging drop preparations as circular and occasionally slightly oval cells, the characters of which do not differ appreciably from those of the yeast just described.

It does not, however, form spores or acid-fast bodies when cultivated for two or three weeks on plaster-of-paris, and slight differences are to be observed in its growth on the various media. When cultivated anærobically the cells undergo precisely similar changes.

On glucose agar it grows rapidly and copiously, producing a heavy, slightly-yellowish white streak, the surface of which is smooth and glistening and rises somewhat abruptly from

the medium, presenting an elevated plane surface in the central portions. When kept for some time the yellowish tinge becomes more marked, but there is no increase in amount after the first week.

On maltose agar the growth is only a little less copious. It is, however, very moist and tends to spread over the medium, and, at the lower part of the culture, looks as if it were flowing down to the bottom of the tube.

On nutrient agar it grows very slowly and scantily. On glycerine agar it forms a narrow, white, glistening streak.

It grows quickly on potato, presenting at first a rather dry-looking white or cream coloured growth with granulated surface, but after a time this becomes very moist and spreads over the medium. The colour does not change much as the culture grows older.

Along the track of the needle in a sugar agar stab culture small colonies appear which do not increase much in size. Growth is free at the surface.

On gelatin minute pin-point white colonies are produced.

It does not grow on blood serum. In peptone beef-broth a white powdery substance is formed and collects at the bottom of the tube.

In fermentation tubes filled with broth, to which one per cent. of glucose, maltose, or lactose was added, it grew very freely in a similar way, but there was no evidence of fermentation at the end of six days.

On maltose agar it produced a thin, scanty, whitish growth when grown under anærobic conditions. Only one small opalescent colony grew on potato under the same conditions.

Inoculation experiments with *S. neoformans* were performed on two mice and four guinea-pigs.

Mouse No. 3 died at the end of twenty-one days.

On the skin of the abdomen there were two roughly circular patches denuded of hair, presenting a dull-red granular appearance. On the surface a little dried secretion could be seen, but no pus. On reflecting the integuments a large flattened tumour was seen presenting a central portion, which was firmly adherent to the skin in the neighbourhood of the patches of ulceration. It implicated the whole thickness of the abdominal

wall, excepting the peritoneum which covered it and outlying portions, which were situated chiefly in the subcutaneous tissue.

TABLE OF INOCULATIONS.

Animal.	Culture used.	Site of Inoculation.	Result.	Pathological changes produced.
Mouse No. 3.	Culture on maltose agar 14 days old.	Abdominal wall.	Death in 21 days.	Circular patches of ulceration on the skin of abdomen, and a large flattened tumour at the site of inoculation. Nodules in great omentum. Enlarged mesenteric glands. Enlarged gland also in mediastinum. Cultures from the tumour, lymphatic glands, and peritoneum were positive.
Mouse No. 4.	Same culture.	Muscles of left thigh.	Death in 26 days.	A large tumour in the muscles of the left thigh, extending posteriorly on to the sacrum. Enlarged glands in the groin and pelvis. Cultures obtained from the tumour.
Guinea-pig No. 5.	Culture on sugar agar 5 days old.	Peritoneum.	Death in 19 days.	No gross lesions.
Guinea-pig No. 6.	Culture on sugar agar 5 days old.	Subcutaneous tissue of the back.	Death in 16 days.	No gross lesions.
Guinea-pig No. 7.	Culture on potato 48 hours old.	Muscles of left thigh.	Killed at end of 6 weeks.	No gross lesions. No cultures obtained.
Guinea-pig No. 8.	Same culture.	Intraperitoneal.	Died in 32 days.	Emaciation and loss of hair. Glands in the groin enlarged. Multiple nodules in the great omentum and on the parietal peritoneum. Nodules in spleen, liver, kidneys, and lungs. Mesenteric and peribronchial glands enlarged. Pure cultures obtained from the peritoneum, kidney, lungs, spleen, and heart-blood.

The whole growth reached from the episternum nearly to the pubes, and extended laterally into the flanks. The peripheral lobules were encapsuled and could be easily removed from the surrounding tissues. The tumour was firm to the touch, and was composed of whitish semi-transparent material resembling the uncooked flesh of fish.

In the great omentum were numerous small white swellings. The kidney, spleen, liver, and lungs shewed no macroscopic change. Enlarged glands were present in the mesentery and anterior mediastinum. Culture tubes were inoculated from the tumour, peritoneal fluid, and heart-blood. They all contained colonies of the yeast, but, with the exception of one tube from the tumour, were contaminated with *B. coli communis* and with cocci.

The other mouse inoculated with *S. neoformans* died at the end of twenty-six days.

In the left thigh, which was the seat of inoculation, a comparatively large tumour had developed. It extended from just above the knee upwards on to the sacrum behind and to the groin in front.

The femur was practically ensheathed in the growth, most of the femoral muscles being lost in its substance. The more superficial muscles lay intact on the surface of the new formation.

The tumour was firmly adherent to the sacrum and, in some parts, to the femur. The glands in the groin and pelvis were enlarged.

Pure cultures of the yeast were obtained from the growth.

Out of the four experiments on guinea-pigs only one gave a successful result. This animal received an injection in the peritoneal cavity of 1 cubic centimetre of an emulsion in sterilized broth of a forty-eight hour culture on potato. It survived thirty-two days, but during the last week it refused food and became very emaciated, losing a great deal of its hair.

After death the glands in the groins were slightly swollen and of firm consistence. The great omentum contained an enormous number of small swellings of varying size, the largest being equal to a split-pea. Many similar nodules appeared in the mesentery, being especially numerous close to the attach-

ment of the latter to the intestine. A few were scattered over the parietal peritoneum and on the diaphragm. These growths were composed of the usual whitish gelatinous material. The spleen was thickly studded with little masses of a similar nature, both on its surface and throughout its substance. The kidneys also contained a good deal of the growth, and one or two nodules were seen in the liver.

Large glands about the size of a horse-bean, of firm, tough consistence, were situated on the posterior abdominal wall, and others were found in the pelvic cavity.

In the lungs a few small miliary nodules occurred, sparsely scattered both on the surface and on the deeper layers.

Two large lymphatic glands lay anterior to the bronchi.

There were no macroscopic lesions in the brain or spinal cord.

The organism was obtained in pure culture from the peritoneum, kidneys, lungs, spleen, and heart-blood, and collections of the parasite were seen in sections of the brain.

(2.) *S. lithogenes.*

Practically no morphological difference was to be observed between the cells of *S. lithogenes* and those of *S. neoformans* in stained or unstained preparations; but there were slight differences to be observed in the method of growth.

Glucose agar was again the most favourable culture ground. On this the yeast formed a broad, raised, white streak, presenting a slight ridge near each border, from which it curved to the level of the medium. Maltose agar also produced a copious growth, which was most raised in the middle of the streak and sloped gradually to its edge. The surface was moist and glistening; and a slightly brownish tinge was acquired as the culture grew older.

On glycerine agar a brilliant white streak was obtained, which was flat and very little raised above the surface of the medium.

The growth on potato was of a light chocolate colour and of the usual character.

On gelatin *S. lithogenes* grew better than any of the other yeasts, producing a narrow, pure white, confluent streak with surface convex transversely.

There was no visible growth on blood serum. No fermentation of glucose, lactose, or maltose occurred, and no spore formation was observed.

The pathogenic action of the yeast was tested on two white mice and two guinea-pigs.

In both mice a yeast septicæmia followed inoculation, and death occurred within four days. In smears prepared from the peritoneal fluid from each animal an enormous number of the yeast cells were present.

TABLE OF INOCULATIONS.

Animal.	Culture used.	Site of Inoculation.	Result.	Pathological changes produced.
Mouse No. 5.	Culture on maltose agar 14 days.	Subcutaneous tissue of the back.	Died in 3 days.	No macroscopic lesions. Cultures of the organisms obtained from the heart-blood and peritoneal fluid.
Mouse No. 6.	Same culture.	Peritoneum.	Died in 4 days.	Some increase in the peritoneal fluid, which was slightly turbid. Cultures obtained from the peritoneal fluid and heart-blood.
Guinea-pig No. 9.	Culture on maltose agar 48 hours old.	Muscles of abdominal wall.	Died in 23 days.	At site of inoculation in the abdominal wall, four small white encapsuled swellings lay in the subcutaneous tissue. The spleen contained numerous miliary nodules. Organism obtained in culture made from the nodules in the subcutaneous tissue and spleen.
Guinea-pig No. 10.	Same culture.	Subcutaneous tissue of the back.	Died in 34 days.	At site of inoculation a small flattened encapsuled tumour containing white semi-fluid material. Enlarged gland in the axilla on both sides becoming caseous. No macroscopic changes in the organs. Cultures were made from the tumour and from the glands. Only one tube from the latter source contained yeast colonies, on the remainder various cocci and bacilli grew.

In guinea-pig No. 9 a chain of four white encapsuled nodules lay in the subcutaneous tissue, white in colour and of firm consistence.

The spleen was infiltrated with whitish transparent granules.

From the tumour and from the spleen the organism was obtained in pure cultures.

Microscopic sections of the new growth revealed the presence of the parasite in great numbers.

In the second guinea-pig inoculated with *S. lithogenes* a small flattened tumour, roughly quadrilateral in shape, 1·2 cm. long and 1 cm. broad, lay in the subcutaneous tissue, slightly adherent to the skin above. It possessed a well-defined capsule and contained soft semi-caseous material. Microscopically the latter was composed of degenerated tissue cells, leucocytes, and a great many large yeast cells with well-marked capsule and granular contents.

In each axilla there was an enlarged gland about the size of a haricot bean, the contents of which were of a precisely similar nature.

No other macroscopic lesions were observed.

Attempts to recover cultures of the yeast from the tumour and glands were unsuccessful, with the exception of one tube inoculated from the swelling in the right axilla.

On all the tubes many colonies of various bacteria were obtained. It is probable, however, that they had invaded the tissues after death, as examination was not made for some hours after the animal died.

(3.) *San Felice's Yeast from an adeno-carcinoma.*

The yeast isolated by San Felice from an adeno-carcinoma of the ovary is morphologically very similar to the other varieties; but here again one may notice slight differences in the character of growth.

In a streak culture on glucose agar it is very similar to that produced by *S. neoformans*, but it is rather a heavier growth and acquires a deeper tinge of yellow.

It grows on maltose agar in the form of a moist, slightly-yellow streak, raised a good deal above the medium, but presenting a central depression. On agar, creamy-white dome-

shaped colonies were slowly produced. The growth on potato was of a *café-au-lait* colour, and much drier than that of *S. lithogenes*.

When cultivated in peptone beef-broth it produced a coherent, almost spherical mass of a greyish-white filmy nature, looking like a small fleecy cloud, which rested at the bottom of the tube and floated upwards when this was gently shaken.

A certain amount of white homogeneous growth adhered to the glass below it. When the tube was agitated more violently the medium became uniformly clouded, and the growth was completely broken up.

The organism grew freely in maltose and glucose broth, the growth collecting at the bottom. No fermentation was observed at the end of six days, and there was no spore formation.

TABLE OF INOCULATIONS.

Animal.	Culture used.	Site of Inoculation.	Result.	Pathological changes produced.
White mouse No. 7.	·5 c.c. of an emulsion of a growth on maltose agar 9 days old.	Subcutaneous tissue of the back.	Died 17th day.	Small white nodule at site of inoculation. Cultures obtained from the nodule and from the heart-blood.
White mouse No. 8.	Same culture.	Intraperitoneal.	Died 3rd day.	Some slightly turbid fluid in the peritoneal fluid, smears from which contained an enormous number of yeast cells. Organisms obtained in pure cultures from the heart-blood and peritoneum.
Guinea-pig No. 11.	1 c.c. of an emulsion of a culture on maltose agar 12 days old.	Intraperitoneal.	Died 13th day.	White nodules in spleen and liver. Slight enlargement of the mesenteric glands. Pure cultures obtained from the liver and spleen and from the heart-blood.
Guinea-pig No. 12.	Same culture and dose.	Subcutaneous tissue of the back.	Died 36th day.	Small tumours at site of inoculation. Swelling, size of a hazel-nut, in the abdominal wall on left side bulging into the peritoneal cavity, with caseating contents. Nodules in the liver. Enlarged glands in the mesentery. Cultures of the organism obtained from the tumours.

San Felice's yeast, isolated from an adeno-carcinoma, was tested on mice and guinea-pigs.

The first mouse, which received ·5 c.c. of an emulsion of this yeast in the subcutaneous tissue of the back, died on the seventeenth day. At the site of inoculation a small, white, firm nodule about the size of a split-pea lay under the skin. This nodule was easily removed from the surrounding tissues. Sections of it examined under the microscope revealed an enormous number of the parasites.

Pure cultures of the yeast were obtained from the nodule, and from the blood in the cavities of the heart.

The second mouse was inoculated in the peritoneal cavity and the animal succumbed on the third day.

The peritoneum contained a small quantity of slightly turbid fluid, the turbidity being due to the presence of the parasites which were exceedingly numerous.

The organism was obtained in pure cultures from the heart-blood and peritoneum.

Guinea-pig No. 11 died on the thirteenth day after injection of 1 c.c. of an emulsion into the peritoneal cavity.

The liver contained five or six white nodules, situated chiefly on the under surface, and extending into the substance of the organ to a depth of about 2 mm. They were roughly spherical in shape and composed of soft gelatinous material.

The spleen was thickly studded with similar growths.

There was slight enlargement of the mesenteric glands.

Culture tubes inoculated from the liver, spleen, and heart-blood gave positive results.

The second guinea-pig, which was inoculated in the subcutaneous tissue of the back, survived the operation thirty-six days. A small flattened tumour was seen in the subcutaneous tissue, measuring 8 millimetres in its greatest length. It was enclosed by a thin capsule, adherent slightly to the skin, and was composed of moderately firm semi-transparent white material.

Lying beneath this, but not communicating with it, was a spherical tumour the size of a hazel-nut, situated in the deeper parts of the abdominal wall and bulging into the abdominal cavity. The peritoneum which covered it was adherent in one place to the lower end of the spleen. Anterior to this the

peritoneum had ulcerated over a very small area, and during manipulation some of the contents of the tumour oozed out at this point.

The tumour was enclosed in a firm capsule, to which muscular fibres from the abdominal wall were adherent. It contained a central yellowish-white core of caseous matter surrounded by more fluid material.

The liver contained two white nodules of a very similar nature.

There was slight general enlargement of the mesenteric glands, one attaining the size of a haricot bean.

The other organs did not present any macroscopic changes.

Cultures of the organism were obtained from all the new formations.

Smear preparations from the softened contents of the tumour in the abdominal wall and in the liver shewed these to be composed chiefly of degenerated tissue cells and leucocytes, with much granular débris. A few of the cells contained yeasts, but a much greater number of these parasites were free, and could readily be distinguished by the presence of the wide clear halo that surrounded each of them.

(4.) *S. tumefaciens albus.*

The cells of Foulerton's *S. tumefaciens albus* were perhaps slightly larger than those hitherto described, and more constantly assumed an oval form.

This yeast grew more rapidly on culture media than any other which I have examined, producing in twenty-four hours on maltose agar a rich, glistening, raised streak of white moist-looking growth, possessing a regular margin and a flat smooth surface. This increases in breadth for the first week and then remains stationary, retaining its white colour and not turning yellow.

Glucose agar also yielded a confluent growth in twenty-four hours, but this was not quite so copious as the above. This streak, which also retained its white colour when kept for some time, presented a median ridge from which the surface sloped gradually to the medium.

Growth on agar was thin and scanty, but developed quickly.

On potato it was copious and of the colour of cream.

On blood serum it formed an opalescent streak, with a ridge running along each margin. After a few days the margin becomes serrated by the formation of narrow tapering outgrowths, which spread laterally over the medium.

The growth in peptone beef-broth was of a white homogeneous nature, lying at the bottom of the tube and leaving the medium above clear. This yeast did not ferment glucose, maltose, or lactose, and no spore formation was observed.

Two mice and two rabbits were inoculated with *S. tumefaciens albus*.

Both mice died within thirty-six hours with a septicæmia.

TABLE OF INOCULATIONS.

Animal.	Culture used.	Site of Inoculation.	Result.	Pathological changes produced.
Mouse No. 9.	·5 c.c. of an emulsion of a 3 days' old culture on maltose agar.	Peritoneum.	Died within 20 hours.	Slight peritonitis; some seropurulent fluid in the peritoneal cavity. Smears from this shewed numerous parasites. Pure cultures from peritoneum and heart-blood.
Mouse No. 10.	Same dose of same culture.	Subcutaneous tissue of the back.	Died in 36 hours.	No macroscopic change observed. Cultures obtained from peritoneal fluid and heart-blood.
Rabbit No. 1.	1 c c. of an emulsion of a culture on maltose agar obtained from mouse No. 9.	Hamstring muscles of left thigh.	Died 33rd day.	Large elongated tumour between the posterior muscles of the left thigh, with white semi-fluid contents. Hydatids in the peritoneal cavity, coccidiosis of the liver. No cultures obtained, but yeasts observed in smears from the tumour at site of inoculation.
Rabbit No. 2.	Same dose of same culture.	Subcutaneous tissue on left side of spine.	Died 27th day.	White encapsuled mass at site of inoculation. Enlarged glands in left groin. Spleen mottled with small white nodules. Cultures of the organism obtained from the tumour and from the spleen.

The parasites in the peritoneal fluid shewed evidence of multiplication, the majority of the cells having produced buds of various sizes.

The first rabbit died on the thirty-third day.

Lying amongst the muscles of the left thigh, at the site of inoculation, was a large irregularly sausage-shaped tumour, about 1¼ inches long, and ½ inch in diameter at its widest part. It tapered somewhat towards each end, and presented one or more lobules extending forwards amongst the muscles. The tumour possessed a thick capsule, which was not very firmly adhered to the structures around it, and contained soft, semi-fluid, almost caseous material.

Smears from this matter contained a large number of yeast cells in various stages of degeneration. No cultures could be obtained. The liver of this animal was extensively affected by coccidiosis.

Rabbit No. 2 died twenty-seven days after the injection of 1 c.c. of an emulsion into the subcutaneous tissue of the back. At this spot a white encapsuled mass was found, roughly circular in outline, and composed of firm, white, semi-gelatinous material.

A gland enlarged to the size of a bean was situated in the groin.

The spleen was mottled with small, spherical, whitish nodules.

Cultures of the parasite were obtained from the tumour at site of inoculation, and from the spleen.

(5.) *Klein's Yeast.*

Klein's yeast appears as rather large cells, usually circular in outline, possessing an average diameter about equal to three-quarters of that of a red blood-cell.

It grows most rapidly on glucose agar, producing a broad flattened streak, not much raised above the medium, with a smooth, glistening, cream-coloured surface.

On maltose agar growth was slower, but eventually became fairly copious. The streak presented a central ridge, from which the growth sloped gradually to the medium. When kept some weeks it acquired a brownish-yellow tinge.

On potato the growth, which possessed the usual character, was of a light chocolate colour.

On gelatin small white colonies developed slowly. On blood serum a faint, slightly-opalescent streak was produced.

In broth this organism grew slowly, forming a white powdery growth which sinks to the bottom of the tube, leaving the medium clear above.

There was no gas production when grown in maltose-glucose- or lactose-broth for five days.

This yeast does not form spores when grown on plaster-of-paris slabs.

Inoculation experiments were performed with Klein's yeast on two white mice, two rabbits, and two guinea-pigs.

One white mouse inoculated in the subcutaneous tissue of the back gave a positive result.

At the site of inoculation there was a flattened tumour, 1·25 cm. long and ·78 cm. broad, lying in the subcutaneous tissue and loosely adherent to the surrounding structures. This swelling, which was unusually firm and hard, possessed a fairly definite capsule, and was composed of firm semi-gelatinous material.

There were three enlarged, white, lumbar glands.

TABLE OF INOCULATIONS.

Animal.	Culture used.	Site of Inoculation.	Result.	Pathological changes produced.
Mouse No. 11.	·5 c.c. of an emulsion of a culture on gelatin 9 days old.	Subcutaneous tissue of the back.	Died 25th day.	Firm, hard, encapsuled tumour at site of inoculation. Three enlarged post-mesenteric glands. Cultures from both sources.
Mouse No. 12.	Same culture and dose.	Peritoneum.	Died 27th day.	No macroscopic change. No cultures made.
Rabbit No. 3.	1 c.c. of an emulsion of a 5-day-old culture on maltoseagar.	Hamstring muscles of left thigh.	Died 19th day.	Small encapsuled tumour at the site of inoculation. Hydatids in the peritoneal cavity. Coccidiosis of the liver. The yeast was obtained in one culture from the tumour.
Rabbit No. 4.	Same culture and dose.	Muscles of abdominal wall.	Died 30th day.	Coccidiosis. No yeast tumours. No cultures obtained.

Animal.	Culture used.	Site of Inoculation.	Result.	Pathological changes produced.
Guinea-pig No. 13.	1 c.c. of an emulsion of a 12 days' old culture on maltose agar obtained from mouse No. 11.	Intra-peritoneal.	Died 25th day.	The animal, which was a full-grown female, appeared well nourished. Around the throat and upper part of the thorax there were about a dozen small, discrete, circular, white nodules adherent to the deeper layers of the skin. Numerous white nodules in the great omentum, white patches on the surface of the kidneys and in the cortex. White nodules on the under surface of the liver and spleen, thickly studded with similar swellings. A mass of small white tumours on each side of the bifurcation of the aorta and in the iliac fossæ. The mesenteric glands were enlarged. Lungs infiltrated with miliary granulomata. Yeasts present in smears from the lesions and cultures obtained from the lungs, peritoneal fluid, and heart-blood.
Guinea-pig No. 14.	A dilute emulsion of a 9 days' old culture on gelatin from mouse No. 11.	1 c.c. in left thigh, 1·5 c.c. in right thigh.	Died 25th day.	The animal was not emaciated. Sores circular in outline around the points at which the inoculation needle entered. Large tumour lying amongst the muscles of each thigh. Large glands in both groins. Pelvis filled with altered, glandular tissue. Nodules in the liver and spleen. Mesenteric glands swollen. Organism obtained in pure culture from the tumours and peritoneal fluid.

Sections of the tumour and glands shewed them to contain an enormous number of the parasites. The organism was also obtained in cultures.

In rabbit No. 3, which was much wasted and probably died from coccidiosis, the only evidence of the pathogenic action of the yeast was the presence of a small white nodule at the site of inoculation, in sections of which the organism was very numerous. One culture made from the tumour was successful.

Guinea-pig No. 13 died on the twenty-fifth day after an inoculation into the peritoneal cavity.

On opening the skin along the median line, a number (about twelve) of discrete, circular, white, flattened nodules were seen adherent to the deeper layers of the skin around the throat and upper part of the thorax. They were firm to the touch, about the size of hemp-seeds, and all lay in an area of one square inch.

The peritoneum contained a small quantity of sticky fluid, but there was no sign of peritonitis.

The intestines were not distended, and appeared normal.

The great omentum contained a large number of firm white nodules varying in size from that of a millet-seed up to that of a pea.

Nodules were especially numerous along the lower border of the stomach. On the surface of the kidneys were a few minute white patches not raised above the surface, but extending into the cortex, which contained other similar patches more deeply situated.

The suprarenal bodies were very large, but appeared otherwise normal.

The liver presented on its under surface nodules similar to those in the kidney, but rather larger.

The spleen was thickly studded with nodules of the same nature throughout its substance. The superficial ones projected somewhat above the surface, giving the organ a mottled and granulated appearance.

A lymphatic gland enlarged to the size of a bean lay on the right side of the spinal column.

On both sides of the bifurcation of the aorta, and extending into the iliac fossæ, was a flattened triangular mass of tissue containing numerous white nodules embedded in loose connective tissues. The nodules contained yeasts in large quantities. Scattered on the surface of the lungs were a large number of small circular patches a little larger than a pin's head. They were slightly raised above the surface, dull-white in colour, and surrounded by a dark purple, almost black, ring.

The tissue of which they were composed lay beneath the pleura, in the form of miliary granulomata, which were scattered freely throughout the whole substance of the organs.

Cultures of the yeast were obtained from the lungs, peritoneal fluid, and heart-blood, and the micro-organism was present in sections of the liver, spleen, kidneys, glands, lungs, and spinal cord.

Guinea-pig No. 14 died twenty-five days after inoculation.

A nine-day-old culture on gelatin obtained from mouse No. 11 was used. The animal received 1 c.c. of a dilute emulsion in the hamstring muscles of the left thigh, and 1·5 c.c. in the right thigh. Swellings developed in both thighs, and small circular red patches about the size of a threepenny-piece developed in the skin at the point of entrance of the needle. These patches were denuded of hair, and presented a dry, dull-red, granular surface slightly raised above the surrounding skin. Little crusts of dried secretion were adherent to the patches; but there was no pus.

Lying amongst the hamstring muscles of the right thigh was a large lobulated tumour, reaching from a little above the knee nearly to the sacrum. It possessed a definite capsule in some parts, but was adherent to the muscles and apparently infiltrated them in other parts; this was especially the case towards the lower end. Above, it became subcutaneous and was very closely adherent to the skin beneath the patches of ulceration. On section it was seen to be composed of firm, white, homogeneous material. There was a precisely similar growth among the flexor muscles of the left thigh. The glands in the groin were much enlarged on both sides, one having reached the size of a large bean. They were composed of material which, in appearance, was identical with that of the tumours in the lower limbs.

The liver presented one or two small white patches on its under surface. There was very little growth in the spleen. The kidneys appeared to be normal. The pelvic cavity was filled with altered glandular tissue of white gelatinous appearance. Similar glands were found in the lumbar region.

The lungs appeared to be normal. There was an enlarged gland in the posterior mediastinum.

The yeast was obtained in pure cultures from the tumours and from the peritoneal cavity.

S. albicans.

S. albicans, when grown on most of the ordinary laboratory media, appears in the form of small oval or round cells possessing the same characters as the yeasts already described.

The average diameter of the cells is about half that of a red blood corpuscle, and very small individuals are common.

If a culture which has been growing on blood serum for twenty-four hours be examined, some of the cells may be seen to have developed narrow, tube-like, hyphal forms of varying length. A constriction usually marks off the hypha from the parent cell. On this medium the mycelial forms do not obtain any great length, and there is no branching.

TABLE OF INOCULATIONS OF S. ALBICANS.

First Culture.

Animal.	Culture used.	Site of Inoculation.	Result.	Pathological changes produced.
Mouse No. 13.	48 hours. 20 hours.	Peritoneum.	Died within 20 hours.	No gross legions except slight peritonitis. Smears from fluid in peritoneal cavity contained numerous parasites in which the mycelial form was well marked. Pure cultures obtained from peritoneal fluid and heart-blood.
Mouse No. 14.	Same culture	Subcutaneous tissue of the back.	Died within 20 hours.	No gross lesions. Smears from peritoneal fluid contained a few parasites. Organisms obtained in pure culture from the peritoneal fluid and from the heart-blood.
Guinea-pig No. 15.	Same culture.	Muscles of left thigh.	Died 4th day.	No macroscopic changes, and no cultures were obtained; but the parasite was present in smears prepared from the peritoneal fluid.
Guinea-pig No. 16.	Same culture.	Peritoneum.	Died 4th day.	Peritoneum contained a good deal of blood-stained, slightly turbid fluid. Many small white or yellowish masses of fibrinous material sticking to the peritoneum in various parts of the abdomen. These masses of fibrinous material contained large numbers of the organism. Mesenteric glands enlarged. No other macroscopic lesions observed. Cultures obtained from the heart-blood and peritoneum.

S. albicans grows well on the ordinary media, and the general character of its growth is of the same character as that of an ordinary yeast.

On maltose agar it produces a thick, white, moist-looking film, which tends to spread over the surface of the medium.

On glucose agar it forms a glistening white streak which is convex transversely and does not spread much.

On glycerin agar moist, circular, dome-shaped colonies appear.

In broth it collects near the bottom of the tube, forming a small filmy spherical mass, on the surface of which minute feathery particles can be seen resting. When the tube is gently agitated, the spherical mass may be made to float upwards, but it soon returns to its original resting-place.

Growth on blood serum resembles that of Foulerton's yeast. A narrow greyish-white streak is first formed from which little spikey outgrowths develop, giving a fringe-like appearance to the margin.

Two different cultures of *S. albicans* were obtained from two different cases of acute pharyngitis in the adult. They were present on the swabs from the throat together with various cocci, and were obtained in pure culture by the plating out method, maltose agar plates being used for this purpose.

The second culture appeared to produce the mycelial forms more quickly on blood serum and to form longer filaments. It sometimes formed hyphæ on potato. There was also a marked difference in the pathogenic action of the two.

Mice inoculated with the first culture of *S. albicans* succumbed within twenty hours.

In the case which received the emulsion in the peritoneal cavity there was some turbid exudation in the peritoneal cavity, with loss of lustre of the surface of the membrane. The parasite was very numerous in smears from this source, and had grown out into long but not branching filaments. A few parasites were present in the peritoneal fluid of the second mouse.

Pure cultures were obtained from the heart-blood and peritoneum in both cases.

Guinea-pig No. 15 died on the fourth day after inoculation in the hamstring muscles. No macroscopic changes could be observed, and all the cultures taken failed, being largely contaminated with putrefactive organisms. In smears, however, the

parasite could be seen in considerable numbers, chiefly in its mycelial form.

More definite results were produced in guinea-pig No. 16, which was inoculated in the peritoneal cavity. Death occurred on the fourth day.

The peritoneum contained a good deal of blood-stained turbid exudation. The membrane itself had lost its lustre and had formed some slight adhesions which, however, were easily broken down.

TABLE OF INOCULATIONS OF S. ALBICANS.

Second Culture.

Animal.	Culture used.	Site of Inoculation.	Result.	Pathological changes produced.
Mouse No. 15.	48 hours' culture on potato.	Subcutaneous tissue of the back.	Died 28th day.	No macroscopic change. No cultures recovered.
Mouse No. 16.	Same culture.	Intraperitoneal.	Died 8th day.	Slight ulceration of the skin at site of inoculation. Beneath the skin a flattened tumour lay over the pubes and hypogastrium; several small nodules in the perineal region. Enlarged glands in the groin. Caseating swelling in anterior abdominal wall. Some peritonitis. Nodules in great omentum and on the peritoneum. White patches in the spleen and liver. Kidneys enlarged and mottled. Nodules in the lungs. Enlarged peribronchial glands. Slight meningitis.
Guinea-pig No. 17.	48 hours' culture on maltose agar.	Muscles of thigh.	Died within 22 hours.	No macroscopic lesions. Smears from the peritoneal fluid revealed the presence of the parasites. Cultures from the kidney, peritoneum, bile, and heart's-blood were absolutely sterile.
Guinea-pig No. 18.	Same culture.	Intraperitoneal.	Killed at the end of 1 month.	No macroscopic lesions. No cultures obtained.

Sticking to the peritoneum in its various parts were large numbers of little white or yellowish masses of fibrinous material of varying size, the largest about equal to a grain of barley. They were scattered scantily over the intestines and over the surface of the liver. In the latter situation the liver tissue appeared to be eroded beneath them, presenting little cup-shaped depressions.

The little masses of fibrinous material contained large numbers of the parasites. The yeast form was more common than the mycelial form.

The mesenteric glands were enlarged.

No other macroscopic lesions were observed.

Cultures of the organism were obtained from the heart-blood and peritoneum.

The second culture of *S. albicans* proved less virulent than the former one.

One mouse survived the inoculation in the subcutaneous tissue for twenty-eight days. No lesions could be discovered after death, nor could the organism be recovered in culture.

The second mouse, which received ·5 c.c. of an emulsion of a forty-eight hour culture intraperitoneally, died on the eighth day from a general infection. There was slight ulceration of the skin at the site of inoculation, and beneath this in the subcutaneous tissue was an irregular, fan-shaped, flattened tumour lying over the pubes and hypogastrium. Its greatest breadth was about 1 centimetre. It was composed of rather soft gelatinous material, and possessed a thin capsule.

Several small nodules were found in the perineum lying along the urethra and round the anus. The testicles appeared to be swollen.

The lymphatic glands in the groin were enlarged.

In the anterior abdominal wall a small white swelling about the size of a split-pea lay beneath the peritoneum. The contents were undergoing degeneration, and were soft and somewhat greasy in consistence. The peritoneum contained a small quantity of turbid fluid.

In the great omentum there were a great many small gelatinous-looking nodules, varying in size from a mustard-seed to a hemp-seed.

Many similar tumours were scattered on the parietal peritoneum and mesentery.

The spleen contained small spherical collections of similar material, and there were adhesions between it and the stomach.

Similar nodules were situated at the surface of the liver.

The kidneys were enlarged and contained numerous small collections of this white gelatinous tissue.

The mesenteric and pelvic glands were enlarged.

The lungs contained a few similar nodules in the surface and deeper in the tissue. The peribronchial glands were much enlarged.

The meninges of the brain appeared inflamed and the blood-vessels engorged with blood.

Guinea-pig No. 17 died twenty-two hours after inoculation into the muscles of the thigh. There were, however, no macroscopic changes, and although the micro-organism could be seen in the smears from the peritoneal fluid and in the lumen of the blood-vessels of some of the organs, all cultures made from the kidney, peritoneum, bile, and heart-blood were absolutely sterile.

The second guinea-pig was killed a month after inoculation into the peritoneal cavity, and the examination gave entirely negative results.

A Non-Pathogenic Yeast.

The yeast obtained in pure cultures from ordinary bakers' yeast was tested on one rabbit and two white mice.

All these animals appeared perfectly healthy after inoculation, and when killed at the end of six weeks no lesions could be seen, nor could cultures of the organisms be recovered. As regards the appearance of the individual cells of this organism on culture media, there was nothing to distinguish it from the pathogenic varieties which have been described. It did not produce filaments when grown on blood serum. It fermented glucose, lactose, and maltose, fermentation of the latter being rather slower than of the first two.

When placed on moist slabs of plaster-of-paris it formed spores within ten days. These spores occurred singly, in twos and in threes, but more commonly in groups of four. They

were circular or slightly oval, and when four were present they were arranged in such a way that each might be regarded as resting on the three others. Around the spores the cell itself appeared as a clear, homogeneous, faintly-staining disc, in which no capsule could be distinguished.

On maltose and glucose agar this yeast produced a whitish moist-looking growth, which was not so copious or heaped up as was that of the other yeasts. It was composed of circular rather flattened colonies with a slightly convex surface, which were confluent in certain parts only.

On agar it formed a scanty opalescent streak.

On potato a thin, cream-coloured growth, similar in character to that of the other yeasts but less copious.

In broth it grew at the bottom of the tube and produced a powdery deposit.

IV.

Description of the Yeast Cells in the Tissues.

(I.) *The New Yeast isolated from Milk.*

Portions of the various tumours produced by yeast infection, and of the organs of the affected animals, were hardened in a 5 per cent. solution of formic aldehyde for forty-eight hours, then dehydrated in alcohol, and finally cleared in cedar oil and embedded in paraffin. For staining the sections and smears, Gram's method and a dilute aqueous solution of methyl violet were employed. The yeast cells retain the purple colour of the aniline gentian violet of the former method after prolonged treatment with alcohol, so that this proved very satisfactory for the detection of the parasite in the tissues, and moreover it brings out very well the morphological changes which the cell undergoes. In addition it possesses an advantage over more elaborate staining methods, in that the materials are always at hand in every laboratory, and the *technique* is known to every student of bacteriology.

Three minutes in aniline gentian violet and one minute in the iodine solution seemed to be sufficient. Eosin was used as

a counter-stain. The disadvantage of the method is that it does not shew up very well the structure of the tissue cells, since eosin does not differentiate the nucleus from the cell body. Brief treatment with hæmotoxylin as a counter-stain obviates the difficulty to a certain extent.

A dilute watery solution of methyl violet, however, gave very good results, and formed an excellent distinctive stain for the parasites. This method was suggested by Foulerton ("Journal of Pathology and Bacteriology," 1900).

The yeast cells stain a bright reddish purple, the tissues a light bluish violet, while the cell nuclei stain a deep purple blue colour.

The blastomycetes become considerably shrivelled and distorted during the process of hardening and dehydrating the tissues, so that the cells are best studied in smears prepared direct from the fresh tissues.

Sections of the tumour at the site of inoculation in mouse No. 1, which forms an example of primary growth produced by the yeast which I isolated from milk, shewed the following characteristics :—

Externally, there is a thin capsule formed by a feltwork of fibrous tissue. The body of the tumour is composed of a loose network of fibrinous ground substance, in which a varying number of mononuclear, round, oval, or fusiform cells are to be seen, and an enormous number of yeast cells, which lie chiefly in the meshes of the network, a few being entangled amongst the fibres of the ground substance. In sections stained with methyl violet most of the micro-organisms appear surrounded by a faintly stained halo, from which fine filaments pass to the neighbouring individuals. Occasionally a yeast cell appears to be suspended in a clear space in the tissues by these strands, which radiate from it to the walls of the space.

The relative proportions of the three chief elements which make up the tissue, namely, the yeast cells, the tissue cells, and the fibrillar ground substance, vary considerably, but the micro-organism nearly always predominates, so that one might justly state that the bulk of the tumour is composed of yeasts.

The organisms vary greatly in size, a very few of the smaller ones being included in the tissue cells; but the greater majority are free.

In smears which were prepared from the fresh tumour and stained by Gram's method, considerable differences could be observed in the morphology of the yeast cells. The majority are stained a very deep purple, their internal structure being more or less obscured. In some, however, one could make out a central zone darker than the remainder, and frequently a dark peripheral zone which represented the double-contoured capsule. The cells varied very greatly in size, from small individuals not much larger than a large coccus, up to cells considerably larger than a red blood corpuscle. (PLATE I., FIGS. 1—8.)

A few were surrounded by a halo of clear material faintly stained with eosin (PLATE I., FIGS. 9 and 10). This is the appearance described by San Felice and others, and named by them the "Hyaline Capsule."

Frequently fine strands or filaments were present passing from a cell to those around it. These strands stained lightly with eosin, and were probably composed of the same material as the hyaline capsule, from which they appeared to arise. (PLATE I., FIG. 7.)

Groups of cells occurred here and there in which the circumference of the individuals appeared flattened or facetted opposite its neighbours, as if they had been pressed together in their growth.

Cells of all sizes might be seen in the act of budding, but they were not numerous. Occasionally one saw a chain of three or more elements, more or less elongated in shape, between which separation had not been completed. More rarely such a chain appeared as a continuous tube (PLATE I., FIG. 21), there being no septa between the elements which composed it. The latter, however, were indicated by swelling of the tube at regular intervals, proving that the appearance was due rather to the incomplete performance of the process of gemmation, than to the production of mycelial forms such as occur in S. albicans.

Though the majority of the yeasts stain uniformly with Gram, there were a large number which did not do so, and in which one could observe marked differences in their morphology.

Some of the cells presented a concentric arrangement. Exteriorly, they were surrounded by a broad, clear zone, often bounded at its circumference by a fairly definite line. This

stained a light pink colour, and sometimes attained a breadth equal to a third or a half of the diameter of the cell within it. Inside the halo one sometimes saw a second zone much narrower than the first, which stained a deeper pink. Within this the protoplasm was filled with fine granules, stained a dark purple colour and disposed in various ways. They were usually very abundant, and massed together at the centre and around the periphery, sometimes at the periphery only. In other yeasts they were less numerous and of large size, and were dotted all over this part of the cell. In yet others they were still larger, and only two or three were present. The ground work of the cell was stained a deep pink colour from the eosin.

In another form which the parasites assumed within the outer halo the cell had taken up a uniform purplish tinge, with sometimes a narrow zone of slightly darker colour at its periphery (PLATE I., FIGS. 16 and 17). In some of these one or more dark granules were present.

This concentric arrangement of the structure of the yeast cell is due to changes which take place in the protoplasm and in the double-contoured capsule. It has already been mentioned that in cells of this yeast which had been grown on blood serum the denser portion of the protoplasm was often seen collected in the centre, leaving a clear space between it and the capsule. In other individuals this refractile material appeared in the form of larger or smaller granules, disposed either centrally or near the periphery. Very similar arrangement may be observed in yeast cells examined unstained in the fresh tissues of an animal. This protoplasmic material is identical with the chromatic granules which have been described.

The double-contoured enveloping membrane or capsule of the older cells from the tissues has a normal appearance when examined fresh; but during the process of drying and fixing the smear, or of hardening the section, this structure often swells to a considerable extent, its breadth becoming greatly increased. Its reaction, moreover, to Gram's staining method varies considerably. In young cells it is coloured deeply by the purple dye, but after it has been in the living tissues some time it may stain either a faint purple or a deep pink with eosin, or remain almost colourless.

It is probable that outside the capsule there is a varying amount of material similar to the zooglœa of bacteria, or of a hyaline substance acquired in some way from the tissues.

The appearance described by certain observers in the "Hyaline Capsule" is due to the swollen refractile capsule itself, and partly, perhaps, to this zooglœa-like substance. That it is not wholly due to the capsule may be inferred from the fact that there are often two zones: an outer, hardly stained at all, and an inner, which takes up a good deal of pink colour from the eosin, and may at times be tinged with purple.

It seems probable that these different forms presented by the micro-organism in the tissues represent different stages in the degeneration of the yeast cells, those which stain deeply with aniline gentian violet being the youngest and healthiest cells.

It will be remembered that when the organism was grown under anærobic conditions for two or three weeks, degenerative changes very similar in appearance to those just described occurred in the cells. Moreover, abnormal or pseudo-mycelial forms were also very occasionally seen. But the so-called "Hyaline Capsule" or clear halo around the cell was never observed under these conditions. The appearance is acquired by the double-contoured capsule in the *tissues of a living animal* only. Both in sections and in smears one only very rarely saw yeasts included in the tissue cells. When this was the case the included parasites were small, and coloured uniformly purple with Gram, and were surrounded by a halo of lightly stained material which represents the capsule.

It is in this condition that the blastomycetes most resemble the so-called "cancer parasites."

In the lymphatic glands infected by the parasite the organisms occurred in very large quantities. In some parts one found them sparsely scattered amongst the lymphocytes in the follicular substance of the gland, which appeared otherwise normal. In other parts the microscopic appearance was identical with that of the tumour just described, that is to say, the normal gland tissue had been replaced by granulomatous tissue which was crowded with yeast cells, small round cells being comparatively scanty.

The extent to which this process had taken place varied greatly. In some glands which were examined, practically the

whole of the organ was transformed into yeast granulation tissue, only a few islets of the original gland tissue remaining.

The appearance of the yeast cells in smears taken from affected lymphatic glands varied a great deal, probably with the length of time the infective process had been going on in the organs, for the particular form which predominated was different in different glands. For example, the yeasts in smears taken from the enlarged bronchial glands of mouse No. 1 nearly all stained deeply and uniformly with the purple dye, and each was surrounded by a well-defined pink halo, which represented the double-contoured capsule. They appeared in groups of from ten to forty or more, and the individuals in these groups were connected to one another by fine filaments. (PLATE I., FIG. 26.)

On the other hand, the majority of the cells obtained from an enlarged gland in the groin of guinea-pig No. 2 were of medium size and very granular, the granules being discrete, and their appearance suggesting an arrangement around the periphery of a spherical cell (PLATE I., FIG. 22). The body of the cell was almost unstained, while each was surrounded by a clear halo of a faint pinkish hue. In the same gland one often saw yeasts which had lost nearly all power of retaining the purple stains, and in which little remained of the cell except the outer halo and some granular débris at the centre. In addition to the form of cell which predominated in any particular gland, other forms not differing from those described in the primary tumours were to be seen in nearly all.

One, however, saw fewer budding cells, and hardly ever pseudo-mycelial forms. Included parasites were rather more common. These last appeared occasionally in the cell substance of the leucocytes, and were almost invariably young individuals which stained uniformly with Gram's method.

The gelatinous nodules which developed in the great omentum were composed of a loose network of fibrinous material containing enormous numbers of yeast cells and relatively scanty tissue cells.

The yeasts were of large size and their contents were usually granular.

In guinea-pig No. 4 the parasite occurred in great numbers in the walls of the intestines. They were seen scattered

amongst the cells of the submucous coat, in the interglandular tissue of the mucous membrane, or in the solitary or agminated follicles. Sections through one of the white nodules which occurred in the ileum, cæcum, and colon, shewed it to be composed of the usual granulation tissue containing multitudes of yeasts. Tissue cells were also relatively numerous.

The growth was bounded on the outer side by the peritoneum, and on the inner side it projected into the lumen of the gut, presenting a ragged, eroded surface, no glands being present over this area. The muscularis mucosæ could be seen intact dividing the growth into two portions.

The kidney contained a great many parasites. The lesions here consist of more or less circular patches of granulation tissue in which the organisms were very numerous, and formed by far the most conspicuous element, while the fibrinous stroma and the round cells were very scanty. These patches varied greatly in size, from those containing only two or three yeast cells, to areas occupying several fields of the microscope. The cortex of the organ was the part chiefly affected.

The kidney tissue around the patches was more or less compressed, so as to form a kind of capsule to it. Except for this the tissue in the neighbourhood appeared normal.

The parasites were arranged uniformly throughout the whole nodule, and were not merely collected at the centre of it.

There was no evidence of inflammatory reaction outside it, although the yeasts were just as numerous at the extreme periphery of the patch as they were elsewhere. They did not, however, appear to wander much beyond the barrier of the flattened glandular tissue. Occasionally, however, one did see an isolated yeast cell in the intertubular tissue and in the glomeruli.

In the liver the blastomycetes were comparatively scanty. Occasionally isolated parasites could be seen lying free in the lobules, apparently situated in the lumen of the capillaries. They also formed well-defined nodules of a similar character to those in the kidneys, the liver tissue being compressed around them into a kind of capsule. Such foci appeared to originate in the intralobular connective tissue.

When the section was stained with methyl violet single

cells would sometimes be seen which presented the appearance of being suspended in the lumen of a capillary by radiating filaments, since these strands stretched from the circumference of the cell to the walls of the space in which it lay.

The spleen was very often much infiltrated with the yeast parasite. Here, again, patches of the typical granulation tissue were seen displacing the normal spleen pulp, to so large an extent in some cases that the bulk of the organ appeared to be composed of these granulomata.

The yeast cells in the spleen were usually of large size, and were frequently granular. Budding cells were fairly common, but pseudo-mycelial forms were absent. Included cells were rather more numerous than in the other organs.

The lungs sometimes contained the parasites in enormous quantities. The lungs of guinea-pig No. 4, for example, were infiltrated throughout with the typical granulation tissue, which appeared to have taken origin in the walls of the alveoli and to have compressed the air cells in their growth. A fair number of the micro-organisms were included in tissue cells; but no giant cells were seen. This yeast tissue did not differ essentially from that in the other organs. The round cells and the fibrinous stroma were relatively scanty.

In the neighbourhood of the yeast foci, one saw some degree of proliferation of the cells lining the alveoli. The blood-vessels appeared to be engorged with blood, and hæmorrhagic areas could be seen, but the parasites were rarely seen in the lumen of the vessels. Patches of emphysema occurred here and there.

In the brain and spinal cord small collections of yeasts were to be seen occasionally. They occurred chiefly in the white matter. They produced small granulomata in which the tissue elements were relatively scanty. No inflammatory changes were to be seen around the foci, and the nervous elements appeared unchanged.

(II.) *S. neoformans.*

The tumours which *S. neoformans* produced at the site of inoculation were practically identical with those produced by the yeast just described. This parasite has been identified in

all the viscera, and the pathological conditions it caused were very similar in distribution and appearance to those described above. Neither did the various forms which the yeast assumed in the tissues differ essentially.

In the primary tumours the average size was perhaps a little smaller, but giant forms were not uncommon.

Chains of cells, in which complete separation of the individuals had not occurred, were very rarely seen.

Not uncommonly one saw cells of medium size which presented a central zone deeply stained by the gentian violet, and a peripheral zone representing the swollen capsule coloured a light purple.

In sections stained with methyl violet the presence of the radiating strands from the periphery of the capsule to the tissues or neighbouring parasites was frequently demonstrated.

(III.) *S. lithogenes.*

S. lithogenes did not produce in the number of animals experimented on so complete a picture of yeast mycosis.

In one guinea-pig firm nodules of the usual type developed at the site of inoculation and in the spleen; but in the second animal they underwent a form of caseous degeneration.

In smears from the peritoneal fluid of a mouse inoculated in the abdominal cavity, the albuminous nature of the fluid was demonstrated by the thin film of clear homogeneous material which it formed on the cover-glass under the action of heat. This took up a certain amount of the pink colouring matter with Gram's method, and in it were to be seen enormous numbers of yeasts staining a dark uniform purple, and each surrounded by a clear unstained space.

In addition to the usual form one not uncommonly saw long thin filaments growing from the cells. These filaments usually presented faint swellings at intervals along their course, indicating, perhaps, that the appearance was not of a true mycelial nature, but the resemblance to a true mycelium was greater than in the case of the first yeast.

The caseating contents of the tumour at the site of inoculation in guinea-pig No. 10 consisted chiefly of leucocytes and mononucleated round cells in various stages of degeneration,

and, in addition, large cells of irregular shape with one or more circular nuclei. These cells usually contained one or more yeasts.

The walls of the nodules were composed of laminated fibrous tissue, with a good many round cells in the meshes.

The parasites were chiefly to be seen in the caseating portions of the swelling, and even in this situation were not so numerous as usual. In sections stained with methyl violet they shewed well-marked strands radiating from the circumference.

In smears from the same source, stained by Gram's method, the parasites all appeared to be of unusually large size, their diameter being at least equal to one and a half times that of a red blood cell; and each was surrounded by a clear, unstained, or faintly pink halo. Some of them stained deeply, often presenting a darker zone between the clear halo and the central part. In the latter chromatic granules were frequently seen. Other individuals stained only a faint bluish purple. Others, again, did not retain any purple colour at all, but were coloured by the eosin. No tendency to the formation of calcareous matter was observed in any of the organs of the animals inoculated with *S. lithogenes*.

(IV.) *San Felice's Yeast from an Adeno-carcinoma.*

The primary tumours produced by San Felice's third yeast, namely, that which he isolated from an adeno-carcinoma, were remarkable for the enormous quantities of the micro-organisms which were present. They composed practically the whole tumour, the tissue elements being reduced to a minimum.

The individual cells stained deeply by Gram's method. A few only had become granular. In smear preparations most of them were encircled by a clear halo. They closely resembled the cells of S. lithogenes as they appeared in the peritoneal fluid of mouse No. 6. This organism has a great tendency towards the development of filamentous forms, or tube-like outgrowths, which as a rule are swollen here and there. These filaments resemble very much the mycelial forms of the oidia, but it seems probable that they also are due to an abnormality in the process of gemmation, in which elongated individuals

continue to be formed seriatim without separation from the parent. These forms were only seen in the primary tumour, and did not occur in ærobic cultures of the organism.

The yeast cells observed in the liver and spleen were of large size, and each possessed a well-marked clear halo. Their contents were granular; and the granules were nearly always collected at the centre of the cell, the remaining portion of the protoplasm being clear.

The tumours at the site of inoculation in guinea-pig No. 9 were of unusually firm consistence. In sections the yeasts were more scanty than usual, while the fibrinous ground substance formed a closer meshwork, and the tissue cells were abundant.

The appearance of the individual yeasts presented no special peculiarity. They were of medium size and stained very darkly. In the spleen of the same animal the parasites were very large and were encircled by a clear halo. In some the protoplasm was filled with large discrete granules.

(V.) *Klein's Yeast.*

Klein's organism gave a very complete picture of yeast infection. It produced large tumours at the site of inoculation, and was found in great quantities in all the organs.

In the primary tumour of guinea-pig No. 14, and in the peritoneal fluid and lymphatic glands of the other animals experimented with, filamentous forms were very numerous and of considerable size. These filaments, like those which have been described, seemed to be composed of yeast cells which had become enormously elongated; but in a few cases they very closely resembled the mycelial forms of *S. albicans*. They were of very variable shape and length. As a rule there was at one end a yeast cell of more normal appearance, evidently the parent of the remainder. From this a long, tube-like process had developed, which was swollen at irregular intervals so that its outline was a series of curves. In breadth it sometimes exceeded the diameter of the parent. Between the consecutive swollen portions the tube shewed more or less definite constriction. This was especially the case between the original cell and its progeny. Occasionally there was lateral branching. The

whole structure possessed a double-contoured capsule, which appeared much swollen in stained specimens, and its inner border ill-defined. Inside the capsule the lumen, which was also of varying width, was sometimes continuous throughout the filament, but, more usually, there were occasional septa dividing it into compartments.

The protoplasmic contents had in most of the cells undergone granular change, and one saw numerous deeply-stained granules collected together, with irregular masses disposed in various ways in the central parts, and frequently along the inner border of the capsule. The staining reaction of these filaments varied in the same way as the yeast cells of ordinary form.

Though most common in the lymphatic glands and primary tumours, these (?) pseudo-mycelial forms were occasionally seen in the metastases in other organs.

With the exception of the unusual frequency of the above, the appearance of Klein's yeast in the tissues did not differ much from that of the other yeasts.

A large proportion of the cells were granular, the granules being collected in the central parts. The remainder of the cell, including the capsule, sometimes stained a pale purple colour with the gentian violet of Gram's method, and sometimes pink with the counter-stain. In the latter structure a faint indication of concentric striæ could sometimes be observed.

When methyl violet was used, fine strands radiating from the periphery were commonly seen, and similar structures staining with eosin were sometimes prominent when Gram's method was used.

This was especially the case in smears prepared from the gelatinous nodules in the peritoneum of guinea-pig No. 13.

(VI.) *Foulerton's S. tumefaciens albus.*

Foulerton's yeast possessed the same general characters as the foregoing, both in its appearance in the tissues and in its pathogenic action.

It killed mice more rapidly than any other, excepting *S. albicans*. The yeast cells observed in the peritoneal fluid of

these animals after death appeared unaltered in their morphology. The organism had evidently multiplied in the tissues with a marvellous rapidity, since countless numbers were present, and a large proportion of those seen were budding.

In the two rabbits inoculated with Foulerton's yeast, large growths developed at the site of inoculation, with, in one animal, secondary foci in the spleen. In the second rabbit the growth was of firm consistence, and possessed the typical histological characters. The yeast cells presented changes in their morphology practically identical with what has been already described.

A clear, faintly stained halo was to be seen around most of the cells, and possessed as a rule a very well-defined outer margin. Occasionally one could observe in this an outer and an inner zone, of which the latter stained more deeply than the former. Very often one could make out a very faint concentric striation in this structure. This yeast often forms chains of three or more elements. They are, however, clearly differentiated from mycelial forms, the individuals composing them being always distinguishable, and, as a rule, septa arising from the capsule can be seen between them.

Rabbit No. 1 survived the inoculation for a longer period, and the tumour became softened and somewhat caseous.

A section through the more solid portions shewed it to be composed chiefly of small round cells, with large oval or round nuclei lying in a more or less scanty network of fibrillar ground substance. (PLATE II.)

The parasites were scattered very sparsely over this portion, but here and there one came upon thickly populated colonies.

In the softening parts of the swelling the round cells appeared degenerated. Large tissue cells with only one nucleus and containing one or more yeasts were seen, and, very occasionally, still larger cells with more than one nucleus.

In smears from the semi-fluid contents the majority of the yeast cells appeared to have undergone advanced degeneration. Frequently one saw only the form of the cell outlined by a narrow band staining pink with eosin, the remainder of the cell being either completely unstained, or presenting a small quantity of a granular material in the centre, which was stained a pale purple or pink colour.

(VII.) *S. albicans.*

S. albicans differs from the foregoing yeasts in that it causes a much more definite inflammatory reaction in the tissues. In one animal only did it produce a tumour at the site of inoculation, namely, in mouse No. 16. This swelling was similar in macroscopic appearance to the neoplasms which have been described. Histologically it was composed of granulation tissue, but the parasites were only numerous in the central portions, and were almost absent from the periphery. Nearly all the micro-organisms were of yeast form and of small size. They were not nearly so numerous as were the yeasts previously described in the neoplastic tissue that they produced. Parasites included in the tissue cells were seen occasionally.

In the abdomen a more or less definite peritonitis was produced. In one guinea-pig this was of a fibrinous nature.

In the mouse mentioned above, granulomata occurred on the peritoneum and in the great omentum. In the former situation they almost invariably assumed the yeast form. In the latter, mycelial forms occurred occasionally.

In the case of the two mice inoculated with the first culture of *S. albicans*, most of the cells obtained from the peritoneal fluid had developed long narrow filaments of uniform breadth, which stained deeply and uniformly with Gram's method.

S. albicans was observed in the liver and kidneys of the same animal. In sections of the latter numerous islets of granulation tissue could be seen situated here and there in the cortex of the organ. At the centre of each, one saw a collection of degenerated cells and débris, amongst which were a large number of the parasites in the form of filaments of moderate length, with granular contents, which formed a loose felt-work. This was surrounded by a broad zone of inflammatory tissue composed of round cells and a scanty fibrillar stroma. At the periphery of this zone the kidney tissue was flattened and formed a kind of capsule to the nodule.

Occasionally isolated parasites, both of filamentous and of yeast form, could be seen amongst the round cells outside the central portion of the tubercle.

V.

Except for *S. albicans*, the pathogenic blastomycetes which have been described present a great similarity both in their biological and morphological characters.

They all appear as round or oval cells. They present similar characteristics when grown on the various culture media. They do not ferment either maltose, glucose, or lactose, and with one exception, of a somewhat doubtful nature, they do not form spores. For the latter reason, according to Hansen's classification, they belong to the group of non-saccharomyces, and should be regarded as torulæ, though this is a term which is rather loosely applied.

When inoculated into animals the pathological conditions they produce are essentially the same. White nodules are found in the subcutaneous tissue and in various organs, which histologically are of the nature of granulomata, but differ from most other granulomata in that the parasite itself forms the bulk of the growth. Occasionally these growths undergo a form of caseous degeneration. This was not noticed with all these yeasts, nor did it always occur with any one of them.

The individual yeast cells undergo morphological changes which vary with the length of time they have been in the tissues, and probably with other conditions not known. The appearance presented by the cells of the different yeasts was essentially the same, except that certain of them shewed a greater tendency to produce, what appear to be, abnormal forms than others.

It was the exception for the parasites to be included in the tissue cells; the large majority were free.

S. albicans differed considerably from the other blastomycetes, not only in its morphology, but in the pathological picture it produced. Its presence in the tissues set up a very definite inflammatory reaction, and the new growth which it produced did not contain the parasite in such large numbers.

As to the identity of the blastomycetes with the so-called cancer parasite, it must be admitted that in certain conditions the yeast cells in the tissues do at times resemble in some

degree the descriptions given of "Cancer bodies" by some writers.

But, on the other hand, whereas the cancer body is almost invariably included in the cells of the growth, the blastomycetes are, as a rule, free in the tissues, and assume a variety of different forms, most of which are not imitated by "Cancer bodies." The staining reactions, moreover, are not identical. Speaking generally, the former take up nuclear stains, while the latter are coloured by protoplasmic stains.

Although a few observers state that they have obtained cultures of blastomycetes from malignant tumours, they only claim to have done so in a very small number of cases. Thus, Plimmer only had one successful case, Roncali three, and Léopold four. Some of these may have been instances of genuine blastomycetic infection, and not carcinoma nor sarcomata at all. For example, Roncali's case, which he describes as an adeno-carcinoma of the transverse colon, may have been a simple yeast infection, since the new growth differed from a malignant tumour in that yeast cells formed a large portion of the bulk of the tissue.

When one takes into consideration how freely the blastomycetes are distributed throughout nature, and how rapidly some at least of them can multiply in the tissues of living animals, it seems strange that accidental infection does not more often occur in malignant tumours, carcinomatous tumours being so frequently developed in parts of the body more or less directly communicating with the outer air.

Attempts to produce malignant growths in animals by inoculating yeast cultures cannot be regarded as successful.

San Felice claims to have obtained two successful cases in dogs. From his description and figures it seems probable that these cases were genuine instances of glandular carcinoma.

When, however, we consider the enormous number of inoculations on various kinds of animals which San Felice performed, one can hardly regard two isolated cases as convincing proof of the alleged action of the blastomycetes in the production of the disease. Even considering the experiments on dogs alone, the results obtained gave a ninety-six per cent. of failures.

San Felice's results, furthermore, fail to satisfy Koch's postulates, since he was unable to recover cultures of *S. neoformans* from the neoplasms.

His explanation of this failure is that the yeast cells which were seen in these tumours were in the form of Russell's fuchsine bodies, in which condition, he states, they are not capable of growing on artificial media ("nicht cultivirbar").

Wlaeff, however, claims to have obtained epithelial tumours in some of his cases by his method of partially immunizing the animal against the blastomycetes, and thus retarding the pathogenic action of the parasite.

Nodules of epithelial origin were observed by Monserrat in animals inoculated with cultures of his yeast, but this author did not consider that they possessed the characters of carcinomata.

It is worthy of note that emaciation, so marked a symptom of malignant disease, was by no means prominent in the inoculation experiments which I have described. In some of the cases, although the animal's body was infiltrated with yeast granulomata, there was apparently no wasting, and fat was present in the subcutaneous tissue.

It seems probable that the blastomycetes produce diseased conditions in man more often than is supposed; for, if we exclude cancer, it would be difficult to explain why an organism so common, and endowed with such marked pathogenic properties, should so rarely be an agent in human pathology.

Moreover, the lesions which yeasts are known to produce often closely resemble those due to other causes. Thus, most of the cases of blastomycetic dermatitis were at first diagnosed as a form of lupus; and the nodule which developed in the organs after experimental inoculation with yeast cultures were very similar to miliary tubercle. The yeast nodules may even, as we have seen, undergo a caseous degeneration which still further increases the similarity.

The larger nodules which developed in the subcutaneous tissue and elsewhere macroscopically resemble some of the commoner forms of new growth, such as sarcoma, and it may be that in man they are responsible for some, at least, of the malignant tumours recognized under this name.

A few successful attempts to isolate blastomycetes from

other forms of disease in man have been made and have been referred to, but whether the organisms had played any active part in the production of these conditions remains uncertain.

It is desirable that a more exhaustive search for such parasites in human pathology should be instituted, in order that their pathogenic action in man may be more fully studied, and that methods of treatment based on a knowledge of their peculiar properties may be tested.

In conclusion, I must thank Mr. Foulerton for his valuable assistance in superintending the work for this Paper, and for performing the inoculation experiments on animals for me.

APPENDIX.

SINCE the foregoing Paper was sent to the press, a further contribution from San Felice* has appeared on the subject of cell inclusions and endo-cellular parasites in malignant growths. The author devotes much space to replying to the criticisms of Nichols, Borrel, and Gaylord on his previous work. These observers, who have ventured to assert that the so-called "Cancer Bodies" are not of the nature of blastomycetes, have, he says, failed to observe and describe the true parasite in the cancer cells, but have mistaken for it vacuolizations of the protoplasm and cell inclusions.

In reply to the objection raised by Nichols and Baumgarten, as to the very small number of successes he obtained in his attempts to produce cancer in animals by inoculating pathogenic blastomycetes, San Felice states that he has had further successes, but does not give any details of them.

In the latter half of his paper he describes minutely the appearances presented by leucocytes which have become included in the cells of carcinomata, and compares them with those due to vacuolization of the cell protoplasm; finally, he contrasts both of these with what he affirms is the true endo-cellular parasite. His descriptions are accompanied with excellent drawings of the three conditions.

The subject of Blastomycosis of the Skin has been ably treated by H. T. Ricketts in a recent paper.† This observer has collected seven cases of "Blastomycetic Dermatitis" from American literature, none which are included in my list. Of these, two appear to be rather doubtful examples. Cultures of budding organisms were obtained in four out of the seven.

Ricketts also describes twelve examples of "Oidiomycosis" of the skin which have come under his own notice. The lesions in these cases closely resemble, both clinically and histologically, those described by Gilchrist, Hektoen, and others. The morbid process is very protracted, and spreads slowly, though more rapidly, than that due to *B. tuberculosis*. The presence of miliary abscesses in the affected skin was a marked feature in every case. In seven of the cases the parasite was obtained in culture, but the organisms appear to have been of the nature of mould fungi rather than true blastomycetes, although in the tissues they assumed a yeast form.

One of the cases Ricketts reports is especially interesting, but unfortunately it was not fully worked out. The patient was a man aged 33, in whom a very chronic affection of the skin of the right shoulder developed. Organisms resembling yeast cells were seen in microscopic sections of the diseased tissue, but repeated attempts to obtain the fungus in culture failed entirely. The man finally died of what was regarded as acute miliary tuberculosis, a diagnosis which was at first supposed to be confirmed by the post-mortem examination. Subsequently, however, Dr. Walker,

* San Felice, "Zelleinschlüsse, Zellentartungen und endocelluläre Parasiten bei bösartigen Geschwülsten." ("Centralblatt für Bakt. u. Parasitenk," bd. xxxi., s. 254.)

† Ricketts, "The Journal of Medical Research," vol. vi., 1901.

who performed the autopsy, examined the lesions more thoroughly, and reported that the nodules in the lung tissue were composed almost entirely of blastomycetes, *B. tuberculosis* being absent.

As to the treatment of this disease, Ricketts states that of the total number of reported cases three have recovered completely, and four others have been greatly improved under the administration of large doses of potassium iodide, combined with the local application of antiseptics. Total excision was entirely successful in two of his cases.

DESCRIPTION OF PLATES I. AND II.

PLATE I.

FIGS. 1 to 21.—Cells of the new yeast (isolated from milk) from the tumour at site of inoculation in Mouse No. 1. (Gram's Stain.)

FIGS. 22 and 23.—Yeast cells from an enlarged gland in the groin of Guinea-pig No. 2. (Same yeast.)

FIG. 24.—Yeast cell from an unstained section of the same gland, shewing the swollen capsule, seen by low illumination.

FIG. 25.—Unusual form from peribronchial gland of Mouse No. 1.

FIG. 26.—Group of yeast cells from the same source.

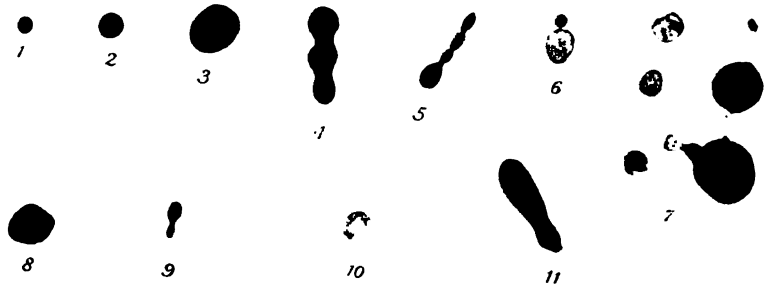
FIG. 27.—Cell from a section stained with methyl violet, shewing delicate strands radiating from the circumference. (Same yeast.)

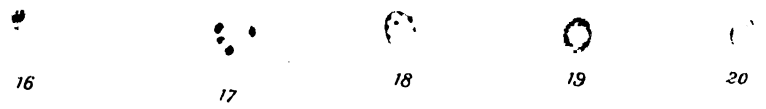
PLATE II.

Section through tumour (Rabbit No. 2) at site of inoculation after an injection of culture of *S. tumefaciens albus* (Foulerton), stained with methylene blue.

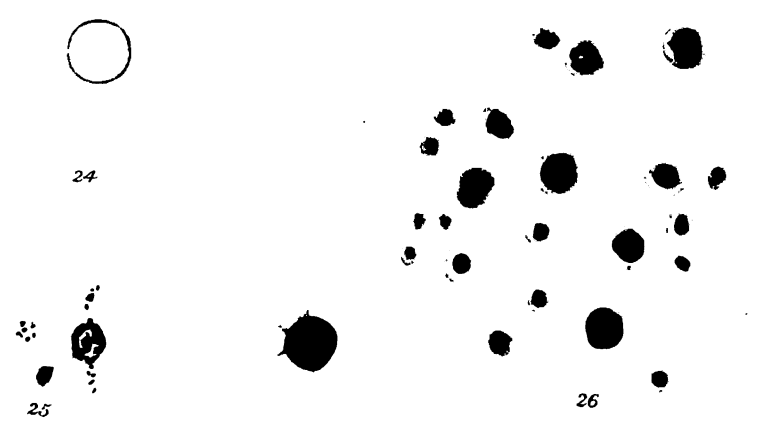
Drawn by H. W. P. YOUNG, *under* ⅛ *objective, No.* 3 *eye-piece.*

PLATE I.



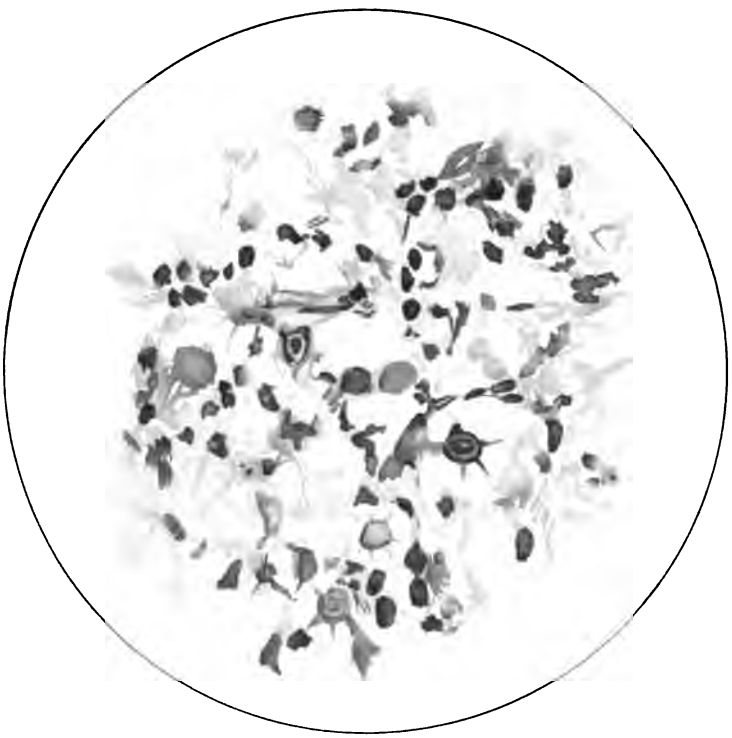


22



Bale & Danielsson, Ltd., Chromo-Lith.

PLATE II



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THE CYTOLOGY OF THE BLOOD IN MALIGNANT DISEASE.

By CECIL PRICE-JONES, M.B.

In the "Dictionnaire de Médicine," published in Paris in 1834, M. E. Littré ([61]) writes: "Je ferai remarquer qu'il n'existe aucun travail sur l'état du sang dans les maladies cancéreuses, et qu'il serait avantageux de connaitre si ce liquide subit une altération, et dans le cas de l'affirmative, qu'elle est cette condition pathologique." Since then nearly seventy years have passed, and to-day pathologists are asking: "Has the mere presence of a malignant growth any direct influence upon the blood of the patient suffering from cancer?" "Are the alterations found in the blood-cells in many cases of cancerous cachexia of a specific nature?" "Is there any evidence to be obtained from the examination of the blood in cancer that can be considered of any diagnostic value?"

This present research on the Cytology of the Blood in Malignant Disease was commenced with a view to a possible solution of these questions.

The following account of the work done must be regarded as strictly preliminary and quite incomplete, being a mere statement of the results of upwards of two hundred examinations of the blood in thirty cases of malignant disease, and the conclusions arrived at are given with the reserve that so limited an investigation implies.

Since the time of Littré, a large number of observers have recorded their observations and results of examinations of blood obtained from cases of malignant disease, and the literature on the subject is correspondingly great; but before the hæmatological researches of Hayem and Ehrlich first placed the cytology of the blood on a firm scientific basis by the introduction of staining methods, and a definite nomenclature and classification of the red and white cells and their varieties, the accounts of

the various authors seem to have interest rather for the medical historian than for the modern pathologist. Though, indeed, the observations of many of these older workers are most careful and accurate, yet their conclusions often suffer in the light of present-day interpretation.

Among the most prominent of earlier writers is Andral (²), who, in his "Essai d'Hematologie Pathologique" (Paris, 1843), gives a very interesting account of the blood in health and disease as then understood. In his account of the examination of cases of malignant disease of various organs (stomach, liver, ovary, uterus), he gives his estimation of the amount of fibrin in the blood of each case, and concludes that, "la fibrine du sang n'augmente que lorsque la matière squirreuse ou encéphaloïde s'avance ou est déjà parvenue à sa periode de ramollisement ou de destruction. Si toutefois par son siége, le cancer compromet les fonctions d'un organe qui sert à la réparation du sang, ou peut trouver dans ce liquide une diminution de la fibrine." Further, he states that the diminution of the blood-cells in cancer only supervenes late, in contrast to tubercular cases, where it occurs at the commencement of the attack; and he remarks, that whereas from the commencement of the illness the phthisical patient is remarkable for his weakness and pallor, it is quite otherwise with cancerous patients. He then considers the question of whether, when cancerous cachexia is well established, the morbid material may not be found in state of detritus in the blood. In conjunction with M. Gaverret he examined microscopically blood obtained, post-mortem, from cases of malignant disease, and in some, "nous avons trouvé au milieu de ce sang des globules de pus trés bien caractérisés. Ces globules ne sont pas sans doubte la matière du cancer; ils sont toute simplement le produit du travail phlegmasique qui, à une certain période de l'existence du cancer se développe dans le tissu où ce produit accidentel a pris naissance." Further, he notes that in a case of osteosarcoma, with extensive mediastinal secondary growth, they found a great quantity of pus cells in the blood of the right ventricle of the heart, and besides these other bodies: "C'étaient des lamelles elliptiques, granitées à leur surface d'un volume beaucoup plus considérable que les globules de pus." They also found these in the "liquide ichoreux," collected from the cancerous mass in the mediastinum.

Paul Broca ([11]) (1852, Paris) quotes the work of Andral and Gavarret, and considers their observations need to be repeated. He thinks their "globules de pus" were not really pus cells but "noyeaux de cancer." However, he apparently examined the blood of patients suffering from various malignant tumours, and at various stages of the disease, and found nothing particular. He says the microscopic examination of blood of cancerous patients, "ne révèle pas grand chose." He gives the results of an analysis of blood from a case of pyloric cancer made by Simon, which shews a diminution of 81·2 per thousand of "globules," an increase of 96·2 of water, albumen and salts being diminished when compared with a normal standard.

Paget ([80]) (1853), in his lectures on surgical pathology, writes: "There is not, so far as I know, anything in the blood of a cancerous person which we can recognize as a cancer structure. . . . . In advanced cases of cancer, and especially in those in which the cancerous substance is very softened and broken, we may meet with portions of it in the blood, which appear as if they had been detached or absorbed from some growth and carried on with the stream." And again: "Neither can we accept, I think, that which is in part a chemical theory, and has been especially held by the pathologists of the Vienna School, namely, that particular diatheses or dyscrases of the blood, appropriate to such diseases as cancer and tubercle, may be recognized by a superabundance of albumen or fibrine. Neither can it, I think, in the present state of organic chemistry, and with so few analyses as we yet possess of the blood of cancerous and other diseased persons, be more than a guess that either cancer or any other such specific disease depends, in any sense, on qualitative modifications of the albumen, or the fibrine, or any other single constituent of the blood."

Lücke ([62]) (1866) found in many cases of malignant disease an increase in white blood-cells, and conceived the phenomenon was pathognomonic of the disease. He mentions a case of lymphosarcoma, in blood from which, taken after death, he found spindle-shaped cells analogous to those found in the tumour. In another place ([63]), referring to the presence of tumour cells in the blood, he says: "Man hat hie und da Beobachtungen über das Vorkommen von Geschwulstzellen im Blute gemacht, doch sind dieselben theilweise unsicher, theilweise anders zu

erklären;" and further, "Bei pigment tumoren hat man schon früher behauptet, im Blute Pigmentzellen und Pigmentschollen gefunden zu haben, und das kreisen von krebszellen in Blut vollen Andral, Keller, Schuh, Rokitansky, Wernher gesehen haben. Es ist nicht zu bestreiten, dass bei diesen Beobachtungen die Fehlerquellen ziemlich häufig sind."

Nepveu ([73]) (1874) noted the presence of pigment granules in the blood of persons affected with melanotic neoplasms.

Sappey ([86]) (1881) found what he considered to be cancer cells in the blood of the veins of an "encephaloid" tumour removed from a mare, post mortem, also in the veins of a large sarcoma removed from a breast. He gives detailed accounts of his procedures, which, however, seem to have been very rough, and his conclusions are open to criticism.

The most recent and important work on the condition of the blood in malignant disease is conveniently reviewed under the five separate headings: I. Hæmoglobin contents; II. Red cells; III. White cells; IV. The question of the leucocytosis of digestion; V. The presence of alleged parasites or specific bodies in cancerous blood.

I.

Among the earlier writers is Leichtenstein ([57]), who observed a more or less diminution of the hæmoglobin contents, and found that this depended on the period of the disease and on the degree of cachexia. He noted in extreme cases a fall of 50—60 per cent. from the normal. He also found that towards the termination of the case there was sometimes a sudden rise in the relative hæmoglobin contents even exceeding the normal value.

Laache ([55]) gives results of four examinations: in two cases of uterine cancer, the hæmoglobin was unaltered in one, and lowered to ·7 in the other; in two cases of cancer of stomach the index was ·46 and ·61 respectively.

Laker ([56]) gives estimations of hæmoglobin in thirty-six cases of malignant disease, and finds that in most cases there is a considerable diminution, but he considers that in general, provided that the patient was not affected by great losses of

blood, the oligochromæmia never reaches so high a degree as is found in tubercular bone disease. In only one case (Parotid sarcoma) did he observe a hæmoglobin percentage of 100. The lowest percentage he found in carcinoma of rectum and uterus. He also observed that in surgical cases the hæmoglobin percentage never returned after the operation to the value it had previously. He considers when the hæmoglobin contents is under 30 per cent. that this is a contra-indication for operation.

Hæberlein ([35]) gives results of seventy-seven observations on seventeen cases with Fleischl's hæmometer. Almost all shew a gradual lowering of hæmoglobin percentage during progress of the case or towards death. He notes two cases of carcinoma ventriculi where the hæmoglobin rose to 105 per cent. and 77 per cent. respectively, but he considers that over 60 per cent. is most exceptional for cancer of stomach, and suggests this as a diagnostic sign in pyloric stenosis. He gives two observations on a case of carcinoma of the pancreas where the hæmoglobin measured 95 per cent. and 87 per cent. respectively.

Neubert ([74]) examined five cases of carcinoma of œsophagus and four cases of carcinoma of stomach. He found the hæmoglobin diminished in each case, and this lowering was not only in percentage but also in corpuscular value (Hb index); but compared with his twenty-four cases of phthisis he finds the lowering of hæmoglobin index is not so great in carcinoma.

Mouisset ([69]) records clinical notes and results of blood examinations in six cases of carcinoma of the stomach, the diagnosis of each being confirmed by post-mortem observation. He found a diminution of hæmoglobin index as marked as in chlorosis. He considers the estimation of the hæmoglobin index as useful in the diagnosis of carcinoma of stomach from pernicious anæmia where the index is normal, or even raised.

Bierfreund ([7]) made hæmoglobin estimations in seventy-two cases of malignant tumours of various natures and situations. They were all surgical cases, and his estimations are taken before and after operation, and on several subsequent days; he makes often over a dozen observations to one case. In eighteen cases, uncomplicated by suppurations or hæmorrhage, the average hæmoglobin contents were 68·5 per cent.; he considers this marked oligochromæmia is the more remarkable as it happened in cases of less advanced disease, in which operation was under-

taken with the best hope for radical cure of the local lesion, and the hæmoglobin stood throughout in no proportionate relation, either to the general condition or to the "ernährung-zustände" of the patients; and he concludes that malignant tumours are associated with an abnormal condition of the blood from quite an early period and in a specific manner. In his fifty-four other, or complicated, cases, the average hæmoglobin contents was only 57·5 per cent. Referring to the regeneration of blood after operation, he found that this required a period of seven days longer in cases of malignant disease than in normal cases. Of his seventy-two patients, he observed a complete regeneration of hæmoglobin in sixty; in none of his cases did the hæmoglobin percentage attain a value higher than that observed before operation.

Osterspey ([79]), in twelve cases of carcinoma of stomach, found the hæmoglobin percentage lowered in eleven cases; he and others refer to Eichhorst, who found a diminution of 40 per cent. of normal, and in one case the hæmoglobin measured only 10 per cent.

Palma ([81]) records a case of sarcoma of the thymus, which shewed a gradual diminution of hæmoglobin during the two months preceding death. The first blood examination gave hæmoglobin about 78 per cent.; a month later it was 65 per cent.; a month later, and two days before death, it was only 33 per cent.

Reinbach ([84]) estimated hæmoglobin in thirty-nine cases, sixteen of which were carcinoma and twenty-three sarcoma of various parts. In each disease the percentage was diminished, averaging in most 45—70 per cent., and in six cases only 18—20 per cent.

Von Jaksch ([48]) reports estimations of hæmoglobin in five cases; the percentage was lowered in each, but apparently in one case the corpuscular value was raised above normal, and in two others it shewed no diminution. His figures are not quite clearly arranged.

Stintzing and Gumprecht ([90]) record three cases of cancer of the stomach. In the first case the hæmoglobin was only 18 per cent., with a corpuscular value of ·47; two months later 15 per cent., and after another six weeks, only 14 per cent.; the second case gave percentages of 46, 42, and 43 on three successive

examinations; and the third case shewed 37 per cent. These writers also record a case of carcinoma uteri, where on three successive occasions the percentage was 29, 28, and 36 respectively. They note that in this case total extirpation of the uterus was successfully performed, and refer to a statement of Mikulicz, that patients with hæmoglobin less than 30 per cent. do not survive major operations.

Hartung ([39]) found marked diminution of hæmoglobin percentage, and also lowering of corpuscular value in ten cases of carcinoma of the stomach.

Von Limbeck ([59]) gives his results of seventeen examinations of the blood from a man suffering from carcinoma of the pylorus, with frequent hæmorrhage, the diagnosis being confirmed post-mortem. During the six months the patient was under observation, the hæmoglobin gradually diminished from 40 per cent. to 25 per cent. He refers also to the two following cases: osteosarcoma of left humerus with hæmoglobin = 28 per cent., and osteosarcoma of sternum = 48 per cent.; but when the red cell count is considered, it is seen that the corpuscular value was raised in both these.

Sailer and Taylor ([87]) examined the blood in twenty-two cases of malignant disease. They found an average hæmoglobin percentage of 35, their extremes being 20 per cent. and 68 per cent., as estimated by Fleischl's hæmometer. They note a very low index in cases of gastric carcinoma.

Lipowski ([60]), in a case of carcinoma of the intestine, found hæmoglobin = 15 per cent. In a case of carcinoma of the liver, he found 35 per cent., with a corpuscular value of ·44, and later 22 per cent., and corpuscular value of ·55.

Osler and Macrae ([78]), from the examinations of fifty-two cases of carcinoma of the stomach, obtained an average percentage of hæmoglobin of 49·9, and a corpuscular value of ·63.

Rieder ([85]) records six cases of carcinoma and four of sarcoma. In the former the average percentage of hæmoglobin was 53, in the latter 51; he notes that during the course of one of the sarcoma cases the hæmoglobin percentage fell as low as 6 per cent.

Cabot ([12]) finds from the notes of hæmoglobin estimation in eighty-seven cases of malignant tumours, the average is 58 per cent.; and comparing this with the average red cell count—

4,140,000—he obtains a colour index or corpuscular value of ·65, which he notes is "distinctly higher than the average of chlorotic cases." The highest cases of his series had 100 per cent. and 90 per cent. of hæmoglobin respectively; and the lowest 20 per cent. and 22 per cent., and in these last the colour indexes were ·36 and ·58 respectively. He states that "as the disease progresses, the red cells and hæmoglobin steadily go down (except in cancer of the gullet)." The colour index usually remains below 1. After comparing the results of his own cases and those of other writers, he concludes that the colouring matter seems more diminished in sarcoma than carcinoma.

Donati ([21]) examined thirty cases of malignant disease; in these the hæmoglobin varied from a minimum of 19·4 per cent. in a case of carcinoma of the cœcum with severe cachexia, to a maximum of 91·6 per cent. in a case of carcinoma of superior maxilla. He considers that the degree of diminution of hæmoglobin percentage depends on the site and on the nature of the malignant tumour, on its stage of development, on its size, and on the presence or absence of metastases.

II.

Most observers have recorded alterations in the red cells, both in numbers and in morphology; but the results are very various, owing generally to the different stages of the disease at which the observations were made, or to the different natures or sites of the disease in the individual cases, so that conclusions drawn from a number of single examinations are of little value.

Patrigeon ([82]) examined the blood in three cases of carcinoma of the body of the uterus and one of the cervix. He concludes that in cancer of the uterus the red cell count is sensibly diminished soon after commencement of the illness, and later it falls to very low numbers; but this statement is scarcely in keeping with the figures given. In his case of epithelioma of the cervix the red cell count, made apparently soon after a severe hæmorrhage, was 3,000,000, and a few days later, after hæmorrhage had ceased, it had risen to 4,000,000. Of his other cases the count is not given in one, is normal or slightly raised (5,000,000) in the second, and in the third case the counts were 4,900,000,

3,500,000, and 4,200,000 in successive examinations; and these may be regarded as within the normal limits for a woman. He records a fifth case of cancer of lumbar glands, liver, stomach, and kidneys, in which he made four examinations, the first being on the eighth day before death with a count of 4,800,000; on the day before death the count was 2,400,000, and on the day of death only 1,800,000.

Laache ([55]), in two cases of uterine cancer, finds the red cell count normal in one and 3,800,000 in the other. In three cases of gastric carcinoma the red cell counts were respectively 2,100,000, 2,800,000, and 4,000,000. He considers that in those cases where the malignant disease is circumscribed, or where the nourishment of the patient is not interfered with, or where there is no great loss from suppuration, there is no remarkable alteration in the blood cell count, and that the longer the period of suppuration and interference with nourishment has existed the greater is the alteration in the blood count.

Hayem ([41]) finds a diminution of red cells in malignant disease, and notes that it is accompanied by a disproportionately rapid diminution of hæmoglobin. But he finds that at the earliest stages of the disease the red cell count is normal, and it is only later, depending on the seat of the tumour, that the red cells are diminished in numbers, sometimes to an extreme degree before death. Referring to the existence of microcytes and macrocytes, he does not consider that they are at all suggestive of cancer. Speaking of poikilocytosis ([42]) he says: "C'est dans la cachexie cancéreuse, consécutive au cancer de l'estomac, que j'en ai vu les exemples les plus remarquables," and he gives a drawing shewing extreme deformities of red cells. He has also noted the presence of nucleated red cells in extreme forms of cancerous anæmia.

Lépine and Germont ([58]) report two cases of cancer of the stomach, in which the blood shewed the presence of a great number of microcytes, and they suggest that this was connected with severe and continual vomiting, since, on subsequent examinations, when this symptom had ceased there were no microcytes to be seen. They refer to two cases reported by Litten where temporary micro-cythæmia was also observed.

Leichtenstein ([57]) observed in many cancerous bloods no change in the red cells, but in others he found marked

poikilocytosis, small diameter cells, microcytes and giant cells, also red cells containing refractile granules.

F. Müller (71) notices a diminution of red cells in a number of cases, in one case as low as 1,200,000. Diminution of red cells has also been observed by Escherich (27), Laker (56), Haberlein (35), Neubert (71), Müller and Rieder (70), Mouisset (69), Osterspey (79), Palma (81), Von Jaksch (48), Zappert (93), Stintzing and Gumprecht (90), Hartung (39), Von Limbeck (59), Dieballa (19), Jez (50), Maragliano (64), and others.

Cabot (12) finds that in all but very advanced cases it is the rule to observe but little diminution in the red cell count; but in the later cachectic stages in most cases there is a quantitative anæmia, running as low as 2,500,000, and occasionally sinking as low as in pernicious anæmia. He refers to the Von Limbeck's (59) case, referred to above, where the red cell count was only 950,000 per c.mm. Of Cabot's own cases the lowest count was 1,457,000. He finds there is no considerable difference between carcinoma and sarcoma as regards their effect on the red cells.

Reinbach (84) found in the majority of his thirty-nine cases the red cell count was not altered, and in several it was over 5,000,000, but in many he gives no figures. He found poikilocytosis in only five cases. In one case—sarcoma of calf of leg—he found one normoblast, but he does not give the number of cells counted in this observation.

E. Grawitz (33) agrees with Laker (56), Leichtenstein (57), Laache (55), F. Müller (71), Von Noorden (75), etc., that the red cell count falls with the progress of the cachexia, and in some cases to a very low value. He finds there are generally morphological changes, *e.g.*, microcytes, macrocytes, and poikilocytes in severe cachexias. He notes a case of cancer of œsophagus, where relatively good nourishment was taken. At the first examination the red cell count was 3,000,000, a month later 2,500,000, and later, just before death, the count was normal or slightly increased. In another place (31) he records a case of cancer of pylorus in an old woman, where he observed a great number of macrocytes, microcytes, and poikilocytes containing granules that had basophile staining; normal sized red cells holding these granules were rare. He found a similar granular condition of red cells in five other cases of carcinoma with cachexia. In this connection may be mentioned a paper by Hamel (37), in which

are recorded blood examinations of eight cases of carcinoma (œsophagus and stomach); in two he found basophile granules in the red cells, in a third case "spärlich," and in a fourth only "vereinzelt"; in the other cases none were observed. Apparently Palma ([81]) observed the same basophile granulation of red cells in his case of sarcoma of the thymus.

An account of the granular and other degenerations of red cells is given by Askanazy ([4]), but his work does not seem to have any direct bearing upon the subject of the present Paper.

Strauer ([91]) found a diminution of red cells which he considered dependent on the progress of the cachexia. He also found much greater degree of poikilocytosis in the later stages of malignant disease than in tubercular cases.

Sailer and Taylor ([87]) in their twenty-two cases found an average red cell count of 3,085,000, and in only four cases above 4,000,000. Microcytes and macrocytes were common in nearly all cases, and in some there was severe poikilocytosis. In ten cases they observed normoblasts, and in one—carcinoma of rectum (clinical history and ? post-mortem not given)—they found microblasts and gigantoblasts. They do not agree with Strauer that poikilocytosis is greater in cancer than in tubercular disease. They observed polychromatophilic cells in a few cases.

Osler and Macrae ([78]), in their fifty-nine cases of carcinoma of the stomach, found an average of 3,712,186 red cells per c.mm.; this they considered high, in consideration of the degrees of cachexia. Twenty-seven of their cases gave a count of more than 4,000,000, and in sixteen the count was less than 3,000,000. In a very acute case with protracted vomiting the count was 6,600,000, and in another much emaciated patient, with very dilated stomach, 6,120,000; the lowest count was 1,168,000, taken six days before death, the post-mortem shewing a large ulcerating growth. A count of only 1,200,000 was observed in a case that shewed many features of pernicious anæmia. They refer to F. P. Henry ([46]), who states that in cancer of the stomach the red cell count never falls below 1,500,000, and that in no case of pernicious anæmia coming to a fatal issue was the red cell count higher than 1,000,000, and that in carcinoma ventriculi the diminution of red cells does not keep pace with the cachexia, whereas in pernicious anæmia the cachexia holds no pace with the oligocythœmia. In connection with the relation of

malignant disease and pernicious anæmia may be mentioned cases recorded by Eisenlohr ([25]), Nothnagel ([76]), Epstein ([26]), Krokiewicz ([51]), Lipowski ([60]), Braun ([10]), and Körmöczi ([53]). Osler and Macrae conclude that in a doubtful case a red cell count below 1,000,000 is strongly in favour of pernicious anæmia. In their more severe cases they observed normoblasts and forms midway between them and megaloblasts, but never typical megaloblasts; and they conclude that while nucleated red cells are present in all very severe anæmias, megaloblasts rarely, if ever, occur in cancer of the stomach, and their presence favours a diagnosis of pernicious anæmia.

Alexandre ([1]) records red cell counts in fifty-seven cases of cancer of various organs. In twelve cases of malignant disease of the stomach there was marked diminution in six, the lowest count being 868,000; in fourteen cases of epithelioma there was marked diminution in three—the lowest 1,643,000 (epithel. cervic. uteri); of his other cases, there was slight diminution in fifteen only.

Donati ([21]) finds in sixteen of his cases a red cell count under 4,000,000, and in nine the count was over 5,000,000, his lowest count being 2,300,000, in a case of carcinoma of the stomach; the same case fifty days later gave a count of 3,712,000, but whereas on the first examination the hæmoglobin index was ·76, on the second occasion it had fallen to ·61. In his conclusions Donati states that in general there is a diminution of the number of red cells, but in a less degree than the diminution of hæmoglobin, the corpuscular value being lower than unity. In his thirty cases he found microcytes in fourteen, and in five he notes poikilocytes. He observed nucleated red cells in none of his cases: in no case did he notice any polychromatophilic cells, and although he searched carefully he never found any red cells shewing basophile granules.

Cabot ([12]) sums up the subject as follows: "1. Small, slow-growing tumours, and the early stages of all tumours may have no effect on the blood appreciable by our present methods of examination. 2. In advanced cases the red corpuscles often become thin, light and pale, and, finally, their number may be greatly decreased, the counts running sometimes as low as in pernicious anæmia. In this respect, as in others, sarcomata seem to injure the blood more than cancers. 3. The colour

index is always below 1, but is rarely as low as we find it in severe chlorosis. 4. Normoblasts and megaloblasts (the latter being in the minority) may occur, the former even in the absence of severe anæmia. Deformities in size and shape (of red cells) are common." Regarding the diagnosis between pernicious anæmia and malignant disease, he says: "(1) Colour index low in malignant, apt to be high in pernicious anæmia. It is often, if not usually, over 1. (2) Leucocytes often increased in malignant, diminished in pernicious anæmia. (3) Lymphocytes often decreased in malignant; increased in pernicious anæmia. (4) Average size of red cells often decreased in malignant, and often increased in pernicious anæmia. (5) If nucleated red corpuscles are present the normoblasts are in a majority in malignant disease, and in a minority in pernicious anæmia." In other words, if the nucleated red corpuscles include a majority of megaloblasts the diagnosis is in favour of pernicious anæmia.

III.

The question of the presence or absence of leucocytosis in the blood of patients suffering from malignant disease has attracted the attention of a great number of observers, and even in those early days before the principles of the modern methods of hæmocytometry, first devised by Vierordt in 1852, were known, many authors, amongst whom may be mentioned Velpeau ([92]), Bérard ([6]), Bouillard ([8]), Follin ([29]), Cruveilhier ([18]), Chaillou ([15]), Ollier ([77]), etc., are referred to by Reinbach ([84]) as having recognized leucocytosis in cancer, but as their methods of blood examination were necessarily of the roughest nature but little value can be placed on their results.

The earliest reliable observations are, apparently, those recorded by Patrigeon ([82]) and referred to above. In his four uterine cases he observed no remarkable increase in the number of white cells, and he concluded that they were not increased under the influence of the disease. In his fifth case, one of cancer of the stomach, liver, lumbar glands, etc., and which he thought was of too complicated a nature to permit of conclusions, he found in the four examinations a gradual rise in white cell count from 6,000 per c.mm. eight days before death up to 27,000 per c.mm. on the day of death.

Escherich ([37]) observed in many cases of the secondary anæmia of carcinoma of various parts a leucocytosis which he found had a direct relationship with the diminution of red cells and their hæmoglobin contents. He states he never observed any connection between the leucocytosis and the onset or intensity of glandular swelling. He also noted in some cases white cells containing hæmoglobin, and also small leucocytes of the lymphocyte variety with neutrophil granules, but from the present standpoint of our knowledge it is difficult to explain what was the significance of these cells.

Potain ([83]) records a case, apparently complicated with leucocythæmia, where there was a high degree of leucocytosis, the ratio of white cells to red cells being 1 : 48; on a later examination, however, this was reduced to 1 : 350. At the post-mortem there was found a large cancerous ulceration of the stomach, the liver fatty, a few grey granulations ("granulations grisses") in the lungs, otherwise all the organs of the body healthy and apparently no signs of secondary deposits.

Klein ([52]) refers to a case of Rosenheim's where the ratio of white cells to red cells was 1 : 40. He considers that leucocytosis increases with ulceration, with the extension of the new growth, and with the growth of metastases, especially of those affecting the cell-producing organs or interfering with the nourishment of the patient.

Hayem ([48]) considers that when it is marked and independent of "phlegmasie infecteuse" the leucocytosis of cancer is of great diagnostic value, although its absence is not against the diagnosis of malignant disease. He thinks that it depends on the exact nature of the disease, and the rate of growth ([44]). He records ([45]) white cell counts in forty-eight cases. In fourteen cases of scirrhus of breast his average leucocyte count was 11,400 per c.mm.; in seven osteosarcomata an average of 19,500; in six epithelioma cases the average was only 7,800, or normal. Of his twelve gastric cases seven shewed no increase, and in five the average count was 17,600. He also notes ([14]) five cases of scirrhus of breast shewing a diminution of leucocytes after operation. One case is very striking: the white cell count before operation was 21,700, five weeks after operation it was only 10,000, and at the date of complete healing of the wound only 6,200; seven months later it had risen to 8,990. In a

case of osteosarcoma of the arm the count fell from 11,250 before operation to 5,270 after complete healing of the wound. He thinks that the examination of the blood may be useful in certain cases to prognosticate a recurrence of the growth, especially after operations where the white cell count had diminished and later again shews increase.

He concludes that with a certain number of tumours there is leucocytosis which constitutes the first sign of the neoplastic cachexia, that it is variable in intensity and seems more marked in certain sarcomata than in carcinomata, and he thinks that all tumours, which, independently of inflammation or suppuration, are accompanied by an increase of white cells, are cancerous tumours. Referring to his note regarding cancers of the stomach, that they class equally into those where there is leucocytosis and those where there is none, and considering the fact that none of his epithelioma cases shewed any marked increase of white cell count, he suggests that those gastric cases which shewed no marked increase of leucocytes may really be epithelioma of the stomach. Speaking ([43]) of the qualitative variations in the white cells, he finds the large mononuclear cells (his variété I.) have a very large, often divided, nucleus, and a protoplasm slightly granular, but *not* with neutrophil granules like the myelocytes of leukæmia; the lymphocytes (his variété II.) acquire a very large size; the polymorphonuclear leucocytes often shew excessive granulation; the eosinophil cells are rare or absent, but it is general to see some mast cells. He thinks these peculiarities are perhaps more constant in cancer than in ordinary anæmias, but they are not pathognomonic.

Alexandre ([1]) from his fifty-seven cases arrives at much the same conclusions as Hayem. He finds a marked increase of leucocytes in the great majority of cases of scirrhus and encephaloid of the breast. He observed the greatest number of white cells in cases of osteosarcoma. He found a leucocytosis in cancers of liver and testicle, but in two cases of scirrhus of pancreas there was no increase of white cells. Of his gastric cases one half shewed leucocytosis, in one case 64,480 per c.mm. The other half gave white cell counts varying within physiological limits. He did not find leucocytosis in any case of epithelioma. He makes no observations as to the relative proportions of the varieties of white cells.

Osterspey ([79]), in his twelve cases of gastric carcinoma, found an increase of white cells in five. He states he could only find a leucocytosis in those cases where the number of red cells was diminished. He concludes that leucocytosis does not always exist, at least at the commencement of the disease, and considers the differences in the white cell counts given by different authors are owing to the different stages at which the blood examinations were made. The following quotation from Virchow has, he thinks, a significant bearing on the question: "Wir treffen leukocytotische zustände in der ganzen Reihe aller Erkrankungen, welche mit Drüsenreizung komplizirt sind, und bei welchen die Reizung nicht zu einer zerstörung der Drüsensubstanz führt. So bald die Drüse abgestorben, käsig geworden oder zerstört ist, so hört auch die Bildung von lymphzellen und damit die Leukocytose auf." Finally, Osterspey, from his own and the observations of others, considers that the blood in carcinoma ventriculi is altered pathologically but not in a specific manner, and does not afford any rule for diagnosis, especially at early stages.

Palma ([81]), in his case of sarcoma of the thymus referred to above, noted in his four examinations white cell counts of 21,224, 9,044, 372,000, and 265,000. The patient was a shoemaker 18 years of age, with enlargement of the inguinal, cervical, and axillary glands of both sides. The illness was rapid, apparently of less than six months' duration. At the post-mortem the diagnosis was primary sarcoma of thymus, with secondary growths in lymphatic glands, liver, and spleen. In dry blood preparations he found enormous numbers of polymorphonuclear leucocytes (moderately granular leucocytes), only a few eosinophils, and some mononuclear cells containing eosinophil granules (? myelocytes). He refers to a case recorded by Fleischer and Penzoldt of multiple swelling of cervical glands (? nature), where an enormous leucocytosis developed, so that the ratio of white cells to red cells was as high as 1 : 9.

Zappert ([93]) records blood examinations in seventeen cases, fourteen being carcinoma of various parts, and three sarcoma. He only found raised white cell counts in five cases: three of these were carcinoma of the stomach, with counts respectively of 10,310, 15,600, and 17,000; in one case of carcinoma of liver he found 10,000; and in a case of sarcoma of the ovary he noted a

count of 21,745. He took special notice of the percentages of eosinophil cells in each leucocyte count, and found on an average their number was below normal; that there is a diminution at approaching death, and that those cases which shewed an increase of eosinophil cells were those in which cachexia is not far advanced, or the illness is of slow progress. Reference to the various normal estimates of these cells will be made in a subsequent section of this Paper.

Müller and Rieder ([70]) found the percentage of eosinophil cells raised in a case of multiple sarcoma of the scalp. They refer to statements made by Ehrlich ([23]) that in all acute leucocytoses the eosinophil cells appear to be diminished, and that an increase of these cells points to a chronic change in the blood-forming organs.

Reinbach ([84]) apparently found leucocytosis in only ten of his thirty-nine cases. From his analyses of the leucocytes he found the relative percentages normal, or differing only inconsiderably from normal, in eleven cases. In the others the relations varied from slight to very high degrees from normal. In the majority of these cases there was an increase of the polymorphonuclear cells with corresponding diminution of the lymphocytes; in the minority was a set of cases shewing an increase of lymphocytes and corresponding diminution of the polymorphonuclear cells. The percentages of the large mononuclear cells and transitional cells accorded with the normal, and similarly with the eosinophil cells, although on two occasions he noted the percentages of these cells at 7·8 (sarcoma of forearm) and 11·6 (abdominal tumours); but he considers the eosinophils have no direct relation to the severity or slightness of the disease. In one case only he observed myelocytes, which had a relative percentage of ·95, but he does not state the number of white cells counted at this examination.

Von Noorden ([75]) states that the white cells are usually increased in the blood of cancerous patients, and relative to the number of red cells they are almost always increased, and that this depends on an increase of the polymorphonuclear cells, though sometimes on an increase of lymphocytes, a condition probably connected with an excitation of the lymph glands in the neighbourhood of the carcinoma (Ehrlich, Einhorn); but if the lymph glands are involved in the cancerous extension and have

their specific action stopped, then the lymphocytes are diminished. He refers to Schneider, who found leucocytosis in each of his twelve cases, noting corpuscular ratios in two cases of 1 : 55 and 1 : 48; also to Pee, who in seven cases found an average white cell count of 18,700; also to other observers (Schafer, Muir, Rieder, etc.). He considers the leucocytosis is due to a chemiotaxis, the white cells being attracted by some substance which has entered the blood from the cancerous growth.

From the observations of Hartung [39], Rieder [85], S. Klein [52], Neubert [74], Krokiewicz [54], Cardarelli [14], Osler and Macrae [78], Lipowski [60], all shewing an increase of white cells in the majority of their cases, it may be noted that the leucocytosis was of the polymorphonuclear variety ("leucocytosis," Grawitz) [33].

Lipowski [60], in his case of carcinoma of the liver, noted no lymphocytes or eosinophil cells after a most careful search, the white cells being all of the polymorphonuclear variety.

Von Limbeck [59] notes that in cancer of the uterus there is usually no leucocytosis, and in cancer of œsophagus the white cell count is often diminished, and shews chiefly small lymphocytes, a condition mentioned by Ehrlich as peculiar to chronic starvation.

Braun [10] records a case described as osteoplastic carcinoma of the prostate with secondary deposits in the bones. Three examinations of the blood were made and shewed a condition closely resembling that found in pernicious anæmia. There was only slight absolute leucocytosis, though the corpuscular ratio at the last count was only 1 : 93; there was a relative increase of the mononuclear over the polymorphonuclear cells, and a large number of mononuclear cells with eosinophil granules, such as are seen in myelogenous leukæmia. He refers to a case recorded by Epstein [26] of carcinoma of the breast with metastases in bone marrow, in which the condition of the blood also in many respects suggested pernicious anæmia. The corpuscular ratio varied from 1 : 25 to 1 : 40; there was also an absolute increase in the white cell count (no numbers given), and there were a large number of mononuclear cells with neutrophil granules (myelocytes). The presence of leucocytosis in cancer cases is of great diagnostic value in those cases in which the condition of the blood resembles that found in pernicious anæmia.

Dieballa ([20]) records ten blood examinations in a case of "sarcoma multiplex cutis," shewing marked increase of white cells (19,000—34,000), which was of the lymphocyte variety ("lymphocytosis," Grawitz), the lymphocytes rising in one count to 94·6 per cent. He seems to regard "lymphocytosis," as opposed to "leucocytosis," as diagnostic of sarcoma. But he refers to Rieder's and Rienbach's cases, where "leucocytosis" was more usual, and also to Chudovsky ([17]), who in nine cases of sarcoma only observed "lymphocytosis" in one.

The results of Sailer and Taylor ([87]) differ in some respects from those of other observers. In their twenty-two recorded cases they found leucocytosis in fifteen, with an average white cell count of 18,000, the highest being in a carcinoma of stomach without metastases. From their differential counts they found an increase of non-granular mononuclear and transitional cells at the expense of the lymphocytes; the polymorphonuclear cells were diminished or not increased (average 66·1 per cent.); in all but five cases the large mononuclear (hyaline) cells were in excess of the lymphocytes. The method of staining is not mentioned. Myelocytes were found in four cases, but the writers could not confirm Epstein's statement ([26]), that the co-existence of myelocytes and nucleated red cells is an indication of bone metastasis.

Cabot ([12]) remarks that the presence of leucocytosis is against the benignness of any tumour, and when no actual increase of leucocytes is present an increased percentage of the polymorphonuclear variety among those present may have the same significance as a leucocytosis. The effects of cancer on the proportion of leucocytes depends upon the position of the tumour, its size, rapidity of growth, the number, size, and position of its metastases, and on the resisting power of the individual. Speaking of myelocytes, Cabot states that he has found them in 50 per cent. of all the cancer cases he has examined.

Donati ([21]) concludes there is a relative and absolute increase of white cells in most cases, and that the seat of the tumour has important bearing on this point. He finds that slow-growing epitheliomas are not accompanied by leucocytosis, but with rapidly developing sarcomas and many medullary carcinomas the condition is well marked. On the other hand, many cases run

a fatal course without any leucocytosis. He thinks that the diminution of leucocytes after removal of the tumour by operation is not constant. In one of his cases he observed that twenty days after the operation there was a slight absolute and relative increase of white cells. In three of his operation cases he notes a slight diminution of lymphocytes as compared with polymorphonuclear cells. In all his cases he only notes an increased percentage of lymphocytes in four. In eleven cases the lymphocyte percentage was diminished; but in most of his cases the relative percentages of lymphocytes and polymorphonuclear cells did not vary from the normal. Invasion of lymphatic glands, he thinks, has not always a special influence on the lymphocyte percentage. He found large lymphocytes were sometimes absent, or very few relatively to the small lymphocytes, but in about half of his cases they were in considerable numbers, amounting to 15—60 per cent. of the lymphocyte white cells, and especially noticeable in cancers of the digestive tract (œsophagus, stomach, cœcum, and rectum). He met with large mononuclear hyaline leucocytes in all his cases, their maximum percentage being 12·48 in a case (recurrent carcinoma of breast) where the lymphocytes were also increased. Three months after operation the percentage of the large mononuclear cells had fallen to 4·7 per cent. He never met with a mononuclear leucocytosis in any case (compare Sailer and Taylor). Speaking of the polymorphonuclear leucocytes (polinucleari neutrofili), he found this percentage raised above 74 per cent. in six cases, lowered below 68 per cent. in eleven cases, and either normal or inconstant in his thirteen other cases. He does not consider that the increase of these cells is proportionate to increase of cachexia, and he is not able to say what special influence the nature, seat, or extent of the tumour has on the increase or diminution of these cells. Of eosinophil cells he found in nine cases a raised percentage above 4·5 per cent., and lowered below 1·5 per cent. in six cases; in two they were absent, and in his thirteen remaining cases they had a normal percentage. He only found mast cells in 30 per cent. of his cases; and refers to Canon, who only found them in two out of four cases, and then only in 0·5 per cent. of white cells; Hayem, on the other hand, states that he usually finds them. In none of his cases did he find any myelocytes, but as in the greater number of his cases he apparently made

only one blood examination, it would seem that some of his conclusions have been formed from rather insufficient data.

Ewing ([28]) considers, "That the carcinomatous process has in itself any capacity to draw leucocytes to the blood may still be doubted, although the edges of the tumour are always inflamed, and adjacent lymph nodes invariably shew inflammatory hyperplasia before metastasis." The leucocytosis is largely owing to complications, such as constantly occur in rapid or advanced cases, and it is therefore unwise to draw any narrow diagnostic conclusions from the presence or absence of leucocytosis. The varieties of leucocytes in carcinoma are found in the same proportions as in other forms of cachectic leucocytosis. Myelocytes occur in many cachectic cases, often in large numbers. There is a relatively greater frequency and extent of leucocytosis in sarcoma cases.

IV.

It is a generally accepted physiological fact, that after a meal rich in proteid the blood of healthy persons shews a more or less increase in the white cell count, averaging about 33 per cent., beginning within the first hour and reaching a maximum about four hours after the taking of the food, and then gradually declining. Rieder ([85]), from observations on twenty-three adults and twelve children, found a maximum increase of 37 per cent. The explanation of this phenomenon is not thoroughly understood, though it is generally ascribed to effects produced by the absorption of food on the mononuclear cells in the adenoid tissue throughout the gastro-intestinal tract, and to an increased outpouring of lymph from the thoracic duct during digestion. But since most observers find this digestion leucocytosis is a mixed leucocytosis, the proportions of mononuclear and polymorphonuclear cells not being greatly changed—in fact the polymorphonuclear cells are more often relatively increased than not—the marrow must furnish a considerable number of neutrophile leucocytes (polymorphonuclear cells), and the chemiotactic properties of the absorbed albumens must be regarded as a possible cause of their increase in the circulation. But although it is the rule, digestion leucocytosis is by no means constantly to be found even in healthy persons, and its

absence is referred to a prolongation of the process from a previous meal, to constipation, or to "accidental causes."

Ascoli (3), in observations on nineteen individuals, found there was a tendency to an increase of white cells, not always, however, higher (17 per cent. to 18 per cent.) than could be explained by errors of observation.

Carstairs Douglas (22), however, in his interesting account of observations made upon himself after a twelve-hours' fast, demonstrated a maximum increase of leucocytes of 95 per cent. four hours after a meal.

In 1890 R. Müller (72) recorded that in observations on five cases of carcinoma of the stomach he was unable to establish a leucocytosis of digestion, and in view of this absence being possibly of great value in diagnosis of malignant disease of the stomach, a number of workers have been directed to this subject.

Hartung (39) examined ten cases of gastric cancer, and in none was he able to observe a digestion leucocytosis. He notes in three cases increases in white cells of 725, 500, and 450, but considers that these may be disregarded. In one case the white cells were diminished. He refers to two cases of mammary carcinoma where digestion leucocytosis was well marked.

Schneyer (88) records eighteen cases of carcinoma ventriculi, in all of which digestion leucocytosis was absent, and he compares these results with eight cases of gastric ulcer and three of non-malignant stenosis, in all of which within an hour after a meal there was an increase of leucocytes varying from 19 per cent. to 59 per cent. Regarding his carcinoma cases it should be noted that only four were verified by post-mortem examination, four others by operation, and of the remaining ten a tumour was felt in seven, and in three he states "Klinische Wahrscheinlichkeits diagnose: Carcinoma ventriculi." He found the degree of cachexia, the presence or not of free hydrochloric acid, and the existence or not of pyloric stenosis, made no difference to his results; so that he considers that the effect is due to anatomical changes in the mucous membrane of the stomach. Whereas in gastric ulcer the disease of the mucous membrane is circumscribed, in malignant disease almost the whole of the mucous membrane is involved.

Marchetti (67) made twenty-four observations in various cases. In two cases of carcinoma of the œsophagus he found well-

marked digestion leucocytosis. In three cases of carcinoma of the stomach he records of one case, at first examination, an increase of 100 white cells after two hours, and at a second examination no change. In another case there was an increase of 100 after six hours at one examination, and a diminution of 100 after six hours on another occasion. In his third case there was a diminution on both observations. He notes also that in a case of cicatricial stenosis (non-malignant) he made seven observations and found no digestion leucocytosis; further, it was also found to be absent in two cases of anchilostomiasis. He concludes that for diagnostic purposes the question must still be left open.

Hassmann ([40]) records two cases, diagnosis being confirmed in one case by post-mortem examination, in the other by operation. In both digestion leucocytosis was present. In one case he noted an increase of 3000 after half an hour, 2000 after an hour, and at another occasion an increase of 2700 after half an hour and 1100 after an hour. In his other case he noted an increase of 1300 after an hour, and a diminution of 300 after two and a half hours later. He does not consider that the presence or absence of digestion leucocytosis is reliable for purposes of diagnosis.

Capps ([13]) examined seventeen cases and found digestion leucocytosis in only two. From the results of all published cases he concludes that it is absent in most cases of gastric cancer, but not invariably so, and that its presence is more against malignant disease than its absence is in favour of that diagnosis.

Hofmann ([17]) records twenty-four cases. In two of these he noted marked digestion leucocytosis, and in a third there was a slight increase; in the remaining twenty-one cases it was absent.

Jez ([50]) reports eight cases, the diagnosis in three being confirmed at post-mortem, and in a fourth there was a palpable tumour and other clinical signs; the diagnosis in the other four cases was unconfirmed. In all of these cases digestion leucocytosis was absent.

Osler and Macrae ([78]) in twenty-two cases note the presence of leucocytosis in ten, its absence in twelve. Of the ten cases in only two was the diagnosis confirmed by post-mortem examination, and in two others "cancerous masses were obtained by stomach tube." In two, death occurred "after a typical course,"

and in the other four cases there was a gastric tumour and other symptoms which excluded error of diagnosis. They doubt its value as a diagnostic sign on account of its uncertainty.

Hayem ([43]) thinks that the blood should be examined with a view to the presence or absence of digestion leucocytosis, but he appears to be sceptical as to the diagnostic value of this phenomenon.

Cabot ([12]) refers to twenty cases, in which digestion leucocytosis was absent in nineteen, but he notes that in ten cases of chronic gastric catarrh it was present only in five—presumably absent in five also. He concludes that on the whole the test is of little diagnostic value.

Ewing ([28]) concludes that from the observations of others "shewing that digestion leucocytosis is absent when the stomach fails either to digest or absorb with considerable activity, conditions which usually but not necessarily accompany carcinoma, but which may also be found in simple ulcer, chronic gastritis, stenosis of pylorus, gastroptosis, anacidity, tuberculosis, etc., it appears that this test can hold only a very subordinate position in the diagnosis of cancer of the stomach."

Carstairs Douglas ([22]) reports eleven cases, "all undoubted instances of malignant disease involving the stomach." He found leucocytosis absent in 54·54 per cent., *i.e.*, in six of his cases, inconstant in one, and present in four cases, or 36·36 per cent. He concluded "that digestion leucocytosis is a broken reed on which to lean in the diagnosis of cancer of the stomach."

V.

It forms no portion of the intention of this Paper to discuss the various alleged parasitic theories as to the etiology of malignant disease which have from time to time been propounded by different observers, but it seems desirable to make some reference to the work of those who have described their "bodies" and "specific organisms" as existing free in the circulating blood.

Kahane ([51]) describes very refractile, irregularly contoured amœboid bodies, some having a rapid rotatory movement, others a direct "sailing" movement. He observed them enter

the red cells and continue their movements in the soft plasma of the same. He considers the granular degeneration of red cells found in cancerous blood is due to the entrance and effects of individual parasites on individual cells. After entering the red cell the "body" appears to sporulate, producing forms which suggest those of the parasite of malaria. The "body" stains with methyl blue—he uses Rosin's method. In the dead state the plasmodia take round contours and are not easily distinguished from blood platelets. He states that in the blood from the neighbourhood of the tumour there are many more "parasites" than in the blood from more distant parts, and concludes from this that the tumour is the seat of origin of the "parasite."

Bra (9) examined the blood in twenty-two cases of malignant disease of various parts, and found his "*champignon* parasite" in both fresh and stained specimens in every case. It occurs as spherical bodies of 1μ—30μ or more in diameter, but more often as spores, which may be free or endoglobular. They are very refractile, have animated Brownian movement, and are stained by Gram's method and safranin.

Chevalier (16) reports that he has isolated from the blood of cancerous patients a "*champignon parasite*," which he succeeded in cultivating in "*bouillon de mamelles de vâche*," glucose broth, agar, serum, gelatine, etc., but he does not appear to have observed either the organism or its spores in the blood itself either in fresh or stained specimens.

Maragliano (65), referring to Bra's "*ascomycete*" and the similar organism of Chevalier, and also to a "*blastomycete*" met with and isolated from the blood by Behla (5), states he has examined the blood from thirty-three cases of malignant disease of various parts, and that in none did he meet any parasites analogous to those found by these observers, and he adds that he worked under conditions identical with those of Bra. In another place (66) he refers to the organism isolated from blood of malignant disease by Francke (30), which was a bacillus identified with that previously isolated by Scheurlen from epithelial neoplasms; also to a motile bacillus with rounded ends isolated from the blood of a negro patient by Freire (31); also to a small micrococcus, which was preferably anærobic, isolated by Moty (68) from the blood of ten cases of

sarcoma; also to Sittmann ([89]), who found a staphylococcus in the blood of a case of carcinoma hepaticæ; and to several others. He then gives an account of nine cases, from each of which he took blood and inoculated various media, and obtained various organisms—staphylococci, streptococci, and long bacilli with slow spiral movements—and he concludes: "*Nel sangue dei carcinomatosi, quando il tumore è ulcerato, si trovano, con discreta frequenza, microrganismi i quali senza avere alcun significato specifico possono dannosamente influenzare il decorso del morbo.*"

Gaylord ([32]) states that the organism described by him as the Protozoon of Cancer, especially the younger forms, can be detected in the peripheral blood of all cases of carcinoma and sarcoma in which there is well marked cachexia, and that animals may be infected by inoculating them with the peripheral blood from cachectic cancer cases when the serum contains the organism. He gives no details of the hæmatological methods he employed, nor does he give any note as to the cellular conditions of the blood in any of the number of blood examinations he has presumably made.

VI.

Methods employed in this research.

From the preceding historical sketch of the more important observations on the blood in malignant disease it is hoped that readers may be able to obtain some general idea of the present position of the subject, which will be seen to shew a trend of agreement with the opinions even of the earlier workers. It appears to the present writer that the chief source of disagreement among the above-recorded observers is the fact that the conclusions at which they have respectively arrived have, in many cases, been founded on single examinations of individual cases. The real influence of a more or less slowly acting pathological process on the blood of a patient can only be determined by repeated observation of the blood of that patient extending over a period of weeks or months, from the first appreciable onset and during the progress of the disease. As far as it is possible this principle has been adopted in this research.

In all cases when possible the examination of the blood consisted in :—

1. The estimation of hæmoglobin percentage.
2. Enumeration of red cells and white cells.
3. The examination of stained blood films, including observation of varieties or abnormalities of red cells and the classification and percentage estimation of the varieties of white cells.

The hæmoglobin was estimated by means of Haldane's [36] modification of Gower's Hæmoglobinometer. In this method the uncertain standard of a column of gelatin, coloured by picrocarmine so as to represent the tint of a 1 per cent. solution of normal blood, is replaced by a dilute solution of blood of known oxygen capacity saturated with coal gas; in other words, the standard is a solution of carboxide hæmoglobin. The blood obtained from the lobe of the ear, or from a finger, is collected in the usual way, and then coal gas is allowed to pass over it for a few seconds so as to convert it into a solution of carboxide hæmoglobin. It is then diluted with distilled water to the required amount and compared with the standard. The advantage of being able to compare the tints of solutions of identical substances is very great, and by this method the error should not exceed 1 per cent.

The cell enumeration was made with Gower's Hæmocytometer, the blood being diluted with Toisson's fluid—a solution of methyl violet, sodium chloride, and sodium sulphate in glycerine and water. In this fluid the red cells take a faint green tint, and the white are stained deep violet. In counting the red cells, twenty, often thirty, and sometimes forty squares were counted at each examination, and an average taken. For the white cells six hundred to one thousand squares were counted. Here it may be noted that the red cell count for healthy men is taken as 5,000,000 per c.mm., and for healthy women as 4,450,000. The physiological limits for the white cells are taken as 5,000—10,000 in both sexes.

In all cases (with a few exceptions) the specimen of blood was taken at the same hour of the day, about 11 A.M. Care was used to avoid all pressure or irritation of the surface from which the blood was taken, so as to retain as nearly as possible the natural condition of the blood in the peripheral circulation, and

for this object no preliminary cleansing or disinfection of the skin was made; and although epithelial cells, grease drops, and various foreign particles were necessarily often present, they could be discounted, and the observations undoubtedly benefited by the more natural state of the specimen. On several occasions, where slight pressure or undue irritation had occurred, the white cell count was noticed to be much increased or altered in character as compared with previous and subsequent counts.

The blood films were made on clean microscopic slides. A drop of blood was caught on the edge of a cigarette paper, or preferably on a clean micro-cover slip, and smeared along the length of the slide, and it was found that after a little practice very thin and evenly distributed films could be obtained by this method. The films, of which several were prepared at each examination, were allowed to dry in the air for a few minutes, no heat being applied, and then fixed and stained by Jenner's stain ([49])—a preparation consisting of a solution of eosin and methylene blue in pure methyl alcohol. The specimens were stained for three minutes, then washed in distilled water until they appeared of a pink colour, and when dry examined with $\frac{1}{12}$ oil immersion.

The nomenclature and classification of the blood cells observed in this research are based on those of Ehrlich, but owing to the variations in terminology employed by various observers it would appear desirable to describe briefly and exactly the appearances of the cells to which the names and classes used in this Paper have been applied. The question of their significance—still in many cases undetermined—belongs to the wider field of general hæmatology, and will therefore not be dealt with in this Paper.

1. *Red Cells.*

(*a*) *The Normal Red Cell* (erythrocyte or normocyte) has a diameter varying in health from 4·5μ to 9·5μ. It stains uniformly with acid dyes, the central concavity appearing lighter coloured.

(*b*) *The Megalocyte* (macrocyte) is a red cell having a diameter considerably greater than the normal—10μ to 20μ. It is frequently deficient in hæmoglobin, and accordingly stains only lightly, often only at the peripheral margin.

(*c*) *The Microcyte* is a red cell with a diameter smaller than normal, varying from 4μ down to 1μ.

(*d*) *The Poikilocyte* is a misshapen red cell, possibly the result of amœboid movements which are said to occur on the degeneration of red cells. This variety has to be distinguished from "artifacts," which often occur as the result of manipulation.

(*e*) *Achromic Cells* (achromocytes), applicable to any of the above varieties where the hæmoglobin is deficient and the cell correspondingly only faintly stained. They present all degrees of pallor down to the so-called "shadow cell," which has only a faint grey, often irregular outline.

(*f*) *Polychromatophilic Cells* are red cells which, instead of staining red, assume a brownish, reddish-blue, or violet tint.

(*g*) *Normoblasts* are normal red cells containing a nucleus.

(*h*) *Megaloblasts* are nucleated red cells of a diameter varying from 10μ to 20μ. When they exceed these dimensions they are termed gigantoblasts. The protoplasm of these cells sometimes shews polychromatophilic staining.

(*i*) *Poikiloblasts*, as the name implies, are nucleated poikilocytes.

2. *White Cells.*

These are grouped into two chief classes, A. (the so-called Hyaline Cells) and B. (the Granular Cells).

Class A. includes three varieties: 1. The Lymphocyte (small and large); 2. The large Mononuclear Cell; 3. The so-called Transitional Cell.

1. *Lymphocytes.*—(*a*) The *Small Lymphocyte*, about the size of the normal red cell, has a relatively large round nucleus usually surrounded by a concentric border of more or less reticulate protoplasm. Often, however, the protoplasm is seen to be extended to one side. It may also give the appearance of being more or less really granular.

(*b*) The *Large Lymphocyte* is quite arbitrarily classed as distinct from the small variety, the distinction being purely a question of cell diameter—often twice that of the smaller variety. Although as a matter of interest they have been separated in all the blood examinations of this research, they will be included in the following account under one variety—*Lymphocytes.*

In normal blood of adults the number of lymphocytes is about 22—30 per cent. of all the white cells.

2. The *Large Mononuclear Cell*, though often described as a large lymphocyte, is readily distinguished from it. Its much greater size is three to four times that of a red cell. Its relatively large amount of protoplasm is often hyaline with faint reticulation, sometimes finely granular. The nucleus is round or oval, rarely indented, and usually eccentrically situated. These are present in normal blood in small numbers, constituting only about 1 per cent. of all the white cells.

3. The so-called *Transitional Cells* are with difficulty distinguished from the preceding variety. The chief distinction rests in their more or less deeply notched or polymorphic nucleus. In the present series of examinations two varieties of these cells have been observed: one in which the protoplasm is hyaline, or apparently nearly so, and the nucleus much divided or in some cases apparently twisted; and a second variety in which the nucleus is only moderately indented (reniform) and the protoplasm distinctly, even coarsely granular. In the following account these so-called transitional cells and the preceding group of large mononuclear cells have been classed together under the name of *Large Mononuclear Hyaline Cells*. In normal blood they form about 2—4 per cent. of all the white cells.

Class B. includes: 1. *Polymorphonuclear Leucocytes;* 2. *Eosinophils;* 3. *Mast Cells;* 4. *Myelocytes.*

1. The *Polymorphonuclear Cells*, or polymorphonuclear neutrophils, are the ordinary leucocytes, and constitute 62—72 per cent. of all the white cells in normal blood. As their name implies the nucleus has many forms. The protoplasm is finely granular, and the granules take a neutral or faintly acid stain. In some cases the granules are more numerous and not so fine.

2. *Eosinophil Cells* are polymorphonuclear, or have more frequently a nucleus apparently divided into two. The protoplasm is usually crowded with very coarse granules which take an acid stain. They constitute 2—4 per cent. of all the white cells in normal blood.

Both of these last varieties, and also the large mononuclear hyaline cells, frequently shew what must be regarded as vacuolations in their protoplasm.

3. *Mast Cells* are polymorphonuclear cells with a clear unstained protoplasm containing—apparently only near the periphery—varying sized coarse granules, comparatively few in number, and taking a dark basic stain, although often not in the pure colour of the dye, but metachromatically. They constitute about 0·5 per cent. of all the white cells in normal blood.

4. *Myelocytes* are mononuclear granular cells, but since they were observed in none of the examinations made for this research they need no attention at the present moment.

No special attention was given to the number of blood plates seen at the different examinations. In some cases they were markedly increased, in others diminished. The subject will be reserved for further notice.

In a great number of cases there were observed apparently organized structures, taking the appearance in some cases of diplococci of various sizes, in others resembling some varieties of yeast cell. The nature of these bodies is as yet not satisfactorily explained, and no reference will therefore be made to them in the remarks accompanying the blood counts. Further work is required in this connection, but so far the present writer has every reason to consider that these bodies are not of a specific nature.

VII.

Blood Examinations of Thirty Cases of Malignant Disease.

The thirty cases are grouped into those affecting the breast, nine; stomach, seven; rectum, three; generative organs, five; tongue, one; larynx, one; one case of melanotic sarcoma; two cases of osteosarcoma; and one case of round-celled sarcoma.

Carcinoma of the Breast.

Case I. (Cancer Register 298, 1901).—Elizabeth B., aged 58. The right breast was removed three and a half years ago; recurrence in scar twelve months later.

On admission in October 1900 she had an ulcerated mass over the mammillary region, œdema of right arm and hand, a tumour in left breast, enlarged glands in both axillæ. She

became gradually weaker, with much dyspnœa for some weeks before her death, which occurred on 12 March 1901, five months after her admission.

Nine blood examinations were made, the last being on the day of death.

Post-mortem examination: Primary growth in right breast; secondary in left breast, axillary, cervical, mediastinal, and mesenteric glands; infiltration of pectoral muscle, sternum,

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1900. Dec. 12.	—	—	20·7	4·1	72	3·7	0	
1901. Jan. 4.	3·2	12·6	12·7	8·9	68·4	9·7	0	2 P.M.
Jan. 11.	3·1	29	21	9	60	10	0	2 P.M.
Jan. 16.	—	—	19·15	10·9	68·19	1·63	0	2 P.M.
Jan. 25.	4·42	12·83	23·18	4·15	70·63	1·52	·55	A few macrocytes, poikilocytes, and achromic red cells.
Jan. 30.	3·76	10·5	22·74	5·32	70·21	1·12	·56	A number of macrocytes and achromic red cells; a few poikilocytes.
Feb. 13.	4·04	12·5	15·25	6·81	73·09	4·81	·4	A large number of macrocytes and achromic cells; a few poikilocytes.
March 1.	4·45	9	14·31	13·15	70·03	1·9	·57	Ten normoblasts in count of over 500 white cells; very large numbers of macrocytes and achromic cells; many poikilocytes; some microcytes.
March 12.	3·8	19·1	10·55	4·15	85	·27	0	Thirty-eight nucleated red cells, of which nine were megaloblasts, three poikiloblasts. There were many macrocytes, and very extreme poikilocytosis.

mediastinum, and pleura. No growth in abdominal viscera or in lumbar or dorsal vertebræ.

Microscopic examination: Growth is a spheroidal-celled carcinoma.

Case II. (Cancer Clinical Register 245, 1901).—Frances H., aged 46. The left breast was removed four years ago; signs of recurrence were first noticed seven months ago.

On admission (8 July 1900) she has hard nodules in the subcutaneous tissue in the region of the scar, at inner side of which the skin is involved and ulcerated. There are numerous other nodules in the subcutaneous tissue over abdomen, back, and neck. There is growth in the right breast, and enlarged tender glands in both axillæ; also painful growths over both parotids, especially left. She has difficulty in opening her mouth, also in swallowing. There are signs of bronchitis over front and back of chest.

Thirteen examinations of the blood were made, extending over a period of more than five months, the majority being at weekly intervals.

The clinical aspects of the case have remained practically unchanged. Occasionally she seemed weaker, took less food, had more pain, and the temperature was raised; but these

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901. Nov. 4.	4·05	9·8	85	1·05	39·03	19·22	40·1	·52	1·05	A few poikilocytes.
Nov. 11.	4·44	9·4	85	·95	32·73	8·83	56·04	·88	1·3	Macrocytes, microcytes, and poikilocytes.
Nov. 18.	3·84	9·3	75	·97	29·07	7·64	61·88	·39	·98	Macrocytes, microcytes, and poikilocytes, also achromic cells.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
Nov. 25.	4·24	9	75	·88	20·95	5·44	71·29	2·05	·22	The same red cell varieties, but patient feels better.
Dec. 2.	3·6	10·8	70	·97	13·4	6·2	78·8	·6	·4	The same red cell varieties. Not feeling so well. Temp. 100° C.
Dec. 9.	4·18	6·7	68	·81	15·33	12·68	68·18	2·27	1·51	Very few poikilocytes. She feels better to-day.
Dec. 16.	3·12	11·3	65	1·04	11	8	79·4	1·4	·2	Poikilocytes and achromic cells. Temp. 101° C. last night; not so well.
Dec. 30.	4·08	14·7	68	·83	16	2·4	78·2	2·2	1·2	Very few poikilocytes. She feels better. Temp. 100° morning, 101·4° evening.
1902. Jan. 7.	4·13	12·5	65	·78	10·75	6·27	82·19	·58	·19	Œdema of L. forearm; not so well. Temp. 100° morning, 101° evening.
Jan. 13.	3·69	9·12	65	·88	18·94	6·23	71·89	2·72	0	Many irregular-sized red cells, and achromic cells.
Jan. 21.	3·57	14·8	65	·91	17·85	3·08	76·42	2·22	0·15	Achromic cells; microcytes; a few poikilocytes.
Feb. 27.	3·61	10·4	65	·90	18·91	2·07	76	2·83	·14	Small diameter red cells; a few microcytes and poikilocytes.
Mar. 18.	4·65	8·5	68	·73	17·39	4·18	75·47	1·67	1·25	Small diameter red cells; a few poikilocytes. Many of the white cells are vacuolated.

symptoms were not lasting. Her chief complaint is the difficulty of eating and swallowing, and the amount of food taken is consequently small.

Case III. (Cancer Register 483, 1902).—Julia C., aged 63. A small tumour was first noticed in left breast about fifteen years ago; it slowly increased and only recently broke through the skin.

On admission (30 November 1901) the left breast is slightly enlarged and fixed to underlying structures, the skin being indurated and ulcerated in places; there are enlarged glands in left axilla, a subcutaneous nodule below the middle of left clavicle, a small indurated mass in inner side of right breast, several enlarged glands in right axilla; liver is nodular and enlarged, extending to within an inch of umbilicus.

She seems strange mentally, complains of no pain, is very feeble, takes very little nourishment; the temperature usually subnormal.

She sank gradually, and died 5 January 1902, five weeks after admission. Four blood examinations were made.

Post-mortem examination: Secondary growths in glands of axilla and neck on both sides, extensive growths in liver, nodules

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks
1901. Dec. 6.	4·27	9	90	1·07	30·6	7·2	60	1	·6	Two normoblasts counted with 500 white cells.
Dec. 13.	4·49	12·6	95	1·08	24·57	7·77	66·98	·31	·31	
Dec. 20.	4·87	9	95	·98	29·5	8·55	61·52	·18	·18	
1902. Jan. 3.	6·39	12·5	95	·75	25·14	3·58	69·05	·56	1·32	Three normoblasts counted with 529 white cells.

on the mesentery, a diffuse growth at the reflexion of the peritoneum from the bladder to the uterus; growth also seen in one of the lumbar vertebræ.

Microscopic examination: Growth is a spheroidal-celled carcinoma.

Case IV. (Cancer Register 326, 1901).—Emmeline G., aged 46. A tumour was first noticed in the right breast in April 1901; the breast and corresponding axillary glands were removed in May 1901; recurrence was noticed in December 1901 in the scar, in the right axillary glands, and above the right clavicle.

On admission (16 January 1902) there are induration and nodules in the neighbourhood of the scar, and enlarged glands in right posterior triangle and axilla. In herself the patient seemed well-nourished and in good health.

Seven blood examinations were made: on the last two occasions she was not so well, having no appetite, complaining of more pain, and not seeming so cheerful as usual; the glands in the neck seemed slightly larger.

Microscopic examination: The growth in the breast and glands was a spheroidal-celled carcinoma.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1902. Jan. 23.	4·25	6·2	80	·95	23·9	·3	75	·6	0	Unequal diameter of red cells. A few poikilocytes and achromic cells.
Jan. 30.	4·32	6	84	·97	17·5	6·15	74·33	1·83	·16	Macrocytes, microcytes, poikilocytes, and achromic cells.
Feb. 6.	4·14	6·7	80	·97	21·05	8·52	68·31	1·13	9.4	Macrocytes, microcytes, poikilocytes, and achromic cells. Seven normoblasts counted with 527 white cells.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
Feb. 13.	4·64	6	80	·86	15·8	12·15	69·49	1·54	·96	Macrocytes, microcytes, poikilocytes, and achromic and polychromatophilic cells. Three normoblasts counted with 518 white cells.
Feb. 21.	4·3	4	85	·98	19·23	4·69	73·82	2·23	0	Macrocytes, microcytes, poikilocytes, and a few achromic cells. Three normoblasts counted with 447 white cells.
Feb. 28.	4·74	6·5	87	·92	14·95	2·07	81·08	1·87	0	Has had urticaria since last week, but is better; a few poikilocytes.
Mar. 7.	4·96	6	87	·88	18·51	3·69	76·02	1·55	·19	Microcytes, poikilocytes, achromic cells, and a few polychromatophilic cells.

Case V. (Cancer Register 503, 1902).—Eliza S., aged 40. Disease was first noticed two years ago, and left breast was amputated in July 1900; recurrence appeared in March 1901. She lost flesh rapidly, and four months ago growth appeared over the right upper jaw, so that she could only open the mouth with difficulty.

On admission (12 January 1902) the left chest is infiltrated with new growth about the scar and in axilla, and there is great œdema of left arm; there are nodules in the right breast and axilla, also in both supra-clavicular fossæ, in submaxillary gland, and in right upper jaw; the mouth can only be opened a quarter of an inch; pain is very great, and she is kept under the influence of morphia; very little food could be taken, and she died 3 February 1902.

Only a single blood examination was made in this case.

Post-mortem examination: New growth in breast, liver, right lung, glands at angle of jaw, axillæ, etc., subcutaneous tissue of chest, gall bladder, both ovaries, etc.

Microscopic examination: The growth was a spheroidal-celled carcinoma.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1902. Jan. 30.	4·79	14·32	82	·87	12·16	2·83	82·83	1·5	·66	Variation in diameter of red cells, but no microcytes, macrocytes, or poikilocytes. A few achromic cells.

Case VI. (Cancer Register 26, 1900).—Agnes S., aged 42. Tumour was noticed in left breast, also discharge from the nipple, seven years ago; the breast was amputated in 1895.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1902. Feb. 7.	4·53	3·8	80	·88	38·16	2·28	57·25	2·09	·19	Some poikilocytes and small diameter red cells.
Feb. 14.	4·86	8·3	80	·82	25·07	3·43	66·8	4·85	0	She has an erythema of both arms; the polymorphonuclear cells are very granular.
Feb. 18.	4·13	5·5	82	1	33·07	1·90	57·03	7·22	·76	Erythema gone. Patient feels better. A few poikilocytes.
Mar. 7.	4·37	10·8	75	·87	39·45	2·67	51·72	5·74	·38	A few achromic cells and small diameter red cells; no poikilocytes.

There was recurrence in scar eighteen months later; this was removed. A few months later there was a second recurrence in axilla; this was removed. In 1900 small nodules were removed from the front of the sternum.

On admission (4 February 1902) she seems in very good health, having only very little pain; there are enlarged glands in left axilla and left supra-clavicular fossa, and a small nodule in front of sternum opposite the third rib.

Case VII. (Cancer Register 404, 1901).—Mary H., aged 64. A growth was first noticed in the left breast four years ago; it gradually increased in size, ulcerated, and has been liable to hæmorrhage for the last two years.

On admission (7 July 1900) there is a hard mass on left breast, not much raised from the chest wall; the area of induration, being about 4 inches by 4½ inches, has a defined raised margin over the middle of the sternum; to inner and upper side of nipple is an ulcerated area about an inch and a half in diameter; the whole mass is firmly fixed to underlying structures; there are enlarged glands in the left axilla—none above clavicle.

At the time the blood examinations were made the case was in a quiescent state. She had greatly improved since admission; the ulceration had nearly healed, and she was thought to be a

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1900. Dec. 19.	—	—	49·7	4·52	39·62	4·49	0	Blood was taken between 2 and 3 P.M.
1901. Jan. 1.	2·1	8	32·6	6	54	7·4	0	„ „ „
Jan. 10.	2·7	5	38·27	10·62	49·8	2·8	0	„ „ „
Jan. 16.	3·7	15	26·73	8·13	61·62	3·48	0	„ „ „

"recovering case." In April 1901 she was not so well. Glands in the right axilla became infected; the ulceration extended to the right side. In May the right breast shewed a number of nodules of new growth, and she died in September 1901.

Post-mortem examination: An ulcerating mass of new growth occupied the left pectoral region, and numerous nodules of new growth were widely disseminated over the chest wall; the left axillary glands were infiltrated with new growth, and there was considerable œdema of the left arm.

Microscopic examination: The growth was a spheroidal-celled carcinoma.

Case VIII. (Cancer Clinical Register 228, 1901).—Sarah Anne T., aged 58. Disease was first noticed four years ago, in 1897.

On admission (6 June 1901) the left breast is represented by an ulcerated area 3½ inches by 2½ inches; in the upper part is a prominent mass (1½ inches by 1½ inches) projecting about one inch from chest wall. This mass is surrounded by a hard slightly-raised edge. There are several infiltrated nodules in the surrounding skin, and hard glands are to be felt in both axillæ.

After treatment with X-Rays considerable improvement occurred, the ulcerated surface healing completely.

Three blood examinations were made at this stage (October).

A later note states that the X-Ray treatment was stopped, and the new surface shewed signs of breaking down again.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901.										
Oct. 9.	4·46	19	—	—	23·03	7·15	68·49	·42	1·05	
Oct. 16.	4·18	9·6	—	—	25·76	9·4	63·86	1	0	
Oct. 23.	4·35	7·7	85	·98	29·42	5·4	63·96	·6	·6	

Case IX. (Cancer Register 431, 1901).—Amelia B., aged 60. Disease was first noticed in 1890 as a small swelling the size of a pea under the right nipple. This gradually enlarged, and, although she was under observation elsewhere from time to time, nothing was done in the way of operation.

On admission in October 1898 the right breast consists of an ulcerating mass firmly fixed to the bony structures beneath; under the skin at the edge of the ulceration are hard fixed masses of growth; the right axillary and supraclavicular glands are hard and enlarged; the left side seems healthy. The breast ulceration increased.

In 1900 symptoms of diabetes appeared, and the patient lost the left great toe from gangrene.

In March 1901 the breast was treated with X-Rays with very good results, the ulceration completely healing over, the hard glands and indurated masses being softer at the time when the three blood examinations were made (October 1901).

She died after a short bronchitic attack on 19 February 1902. The post-mortem examination shewed a small, hard, subcutaneous nodule at the edge of the healed ulcer, small deposits of growth in both axillæ and at back of sternum; there was acute bronchitis in both lungs.

Microscopic examination: The growth was a spheroidal-celled carcinoma.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901.										
Oct. 16.	4·87	11·72	—	—	24·88	5·36	65·02	3·64	·85	
Oct. 23.	4·68	9·6	80	·86	30·65	4	60·17	4	1·14	
Oct. 27.	4·45	7·25	85	·96	28·8	5·6	60·8	3·8	1	

Carcinoma of the stomach.

Case X. (Cancer Register 283, 1901).—Robert T., aged 61. For two years he has had epigastric pain after taking food, relieved by vomiting. For five months there has been considerable loss of flesh.

On admission (29 January 1901) he presents great pallor, emaciation and feebleness, vomiting only occasional, and pain was less marked than during earlier stages of the illness. There is fulness of the epigastric and left hypochondriac regions, and a sense of deep resistance on palpation. To left of umbilicus there is a hard irregular mass moving with respiration. There are numerous small, hard, subcutaneous nodules of the size of a split-pea over the abdomen.

He became rapidly weaker, and four days before death (10 February) the cartilaginous portion of the nose and the toes of both feet presented a uniform deep purple colour, resembling an appearance met with in Raynaud's Disease. Only one blood examination was made three days before death.

At the post-mortem made on 11 February the lesser curvature of the stomach near the pylorus was infiltrated with new growth, which also extended backwards, involving the prevertebral glands. There was no evidence of any other metastases besides the subcutaneous nodules above mentioned.

Microscopic examination: Sections from the stomach, aortic glands, and subcutaneous nodules shewed a glandular carcinoma

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901. Feb. 7.	1·46	24·5	33·33	12·28	50·76	3·59	0	A large number of macrocytes, microcytes, poikilocytes, and achromic cells. A large number of nucleated red cells, 37 per cent. of which were megaloblasts.

undergoing colloid degeneration. The subcutaneous nodules consist of almost pure colloid material.

N.B.—This case was read by Dr. Pasteur at the Clinical Society on 10 May 1901. In that account certain cells were enumerated and figured as "basophil myelocytes." In this research these cells are regarded as "granular transitional cells" (see p. 142), and in the above table are included among the large mononuclear cells.

Case XI. (Cancer Register 453, 1901).—Marie G., aged 70. Epigastric pain and vomiting after food commenced ten months previous to date of admission (25 September 1901).

She is very emaciated, and the skin is rather pigmented. There is a mass to be felt in the epigastrium about three inches in diameter; it moves slightly with respiration. She vomits almost every day and seems to keep very little food down.

From 14 October X-Rays were applied to the surface of the abdomen for fifteen minutes five days a week. She remained in about the same condition until 24 November, when she had sudden acute pain in abdomen and died two days later.

At the post-mortem examination there was found a perforation of the anterior wall of the stomach about three inches from the pylorus. The stomach wall was occupied in its

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901. Nov. 1.	3·49	10	38	·55	23·26	1·63	74·48	·61	0	Extreme poikilocytes, macrocytes, microcytes, and achromic cells.
Nov. 8.	3·12	8·71	30	·48	19·88	7	72·26	·56	·28	Ditto.
Nov. 15.	3·97	8·6	36	·45	25·09	5·54	69·07	·13	·13	Ditto.
Nov. 22.	3·02	7·6	35	·57	31·13	2·07	66·22	·18	·37	Ditto.

circumference by a nodular growth, about one inch wide at the lesser and three inches wide at the greater curvature, and situated about an inch from the œsophagus. Along the attachment of the small intestine to the mesentery are some minute white hard growths; no other secondary deposits noticed.

Microscopic examination: The growth was a columnar-celled carcinoma.

Case XII. (Cancer Clinical Register 291, 1901).—Sarah D.,* aged 64. Has been ailing for three years, losing flesh and having occasional attacks of vomiting. Four months ago a severe attack of diarrhœa, with stabbing pain in the stomach extending to shoulder and down left side.

On admission (30 November 1901) she is much wasted and has a sallow yellow complexion. A tumour can be felt to the left of the umbilicus; it moves with respiration and is rather tender on pressure. She takes but little nourishment, but has not vomited since admission; the bowels are always loose. Her condition is unaltered after four months.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901.										
Dec. 10.	2·98	21·6	30	·51	11·37	9·38	77·38	·99	·85	Achromic and polychromatophilic cells, a few poikilocytes, macrocytes, and microcytes.
Dec. 18.	2·95	14·5	30	·51	20·37	2·86	75·5	1	·25	Ditto.
1902.										
Jan. 1.	3·03	15·2	25	·41	18·25	4·25	76·79	·33	·33	Ditto. Red cells are very pale.
Jan. 8.	3·08	16·3	20	·33	14·51	3·17	81·63	·68	0	Ditto.

* This patient died 14 April 1902 with numerous secondary nodules of new growth in her liver, gall-bladder, and pancreas. The primary new growth was in the stomach, and was a columnar-celled carcinoma.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
Jan. 15.	2·59	12·75	25	·50	14·06	4·32	81·22	·36	0	Ditto. No polychromatophilic cells.
Jan. 22.	2·99	11	20	·36	25·1	1·16	72·6	1	0	Increased poikilocytosis. Three normoblasts with 600 white cells.
Jan. 29.	2·85	16·2	22	·39	22·01	1·44	75·81	·54	·18	Ditto. No normoblasts seen.
Feb. 5.	2·63	12·2	25	·48	20·38	·64	77·66	1·29	0	Ditto. Three normoblasts to 618 white cells.
Feb. 12.	2·87	13·75	28	·49	14·4	·8	84·4	·4	0	Left leg and ankle swollen. Four normoblasts to 500 white cells.
Feb. 20.	2·19	10	20	·47	22·14	1·05	75·94	·63	·21	Leg still swollen. Much poikilocytosis. Two normoblasts to 474 white cells.
Feb. 27.	2·52	11·2	22	·44	22·5	·74	75·75	1	0	Ditto. No normoblasts seen.
Mar. 6.	2·86	13·3	26	·46	25·33	1·87	71·42	1·36	0	Ditto. Three normoblasts to 588 white cells.

Case XIII. (Medical Register 1388, 1901).—Annie F., aged 42. She has had epigastric pain and vomiting after taking solid food during the last five months, but latterly the pain has been constant and more extensive, and during this time she has rapidly lost flesh.

On admission (31 December 1901) there is felt a hard mass above and to right of umbilicus, with a raised rounded upper margin which moves with respiration.

On 10 January gastro-jejunostomy was performed. The tumour was found at the pylorus; there were several enlarged glands.

She made a good recovery from the operation and was discharged on 26 February, vomiting and pain having ceased and the patient able to take good nourishment.

Date.	Red Cells in Millions per c.mm.	White cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901. Dec. 31.	4·61	8·7	80	·86	30·01	4·88	63·69	1·06	·42	
1902. Jan. 7.	4·87	10·4	75	·78	34·73	4·19	59·73	·88	·44	
Jan. 13.	4·76	8·75	85	·9	22·4	4·2	71·6	·8	1	Three days after operation; a few poikilocytes, achromic and polychromatophilic cells. Seven normoblasts to 500 white cells.
Jan. 21.	4·3	9·6	88	1·02	25·3	3·06	70·52	·9	·18	A few poikilocytes, microcytes, and achromic cells, but no polychromatophilic cells. One normoblast to 553 white cells.
Feb. 3.	3·6	9·5	80	1·1	21·88	·69	76·03	·69	·69	Left ankle swollen. Temperature 102° C. Only a few poikilocytes.
Feb. 10.	3·87	7·6	75	·98	15·62	·12	81·25	1·6	·2	Ankle and leg in bandage. Very slight red cell change.
Feb. 17.	4·33	10	75	·87	27·39	6·25	64·57	1·36	·39	Eats meat; gets up; feels very well; no red cell changes.

Case XIV. (Medical Register 42, 1902).—Thomas G., aged 56. First had stabbing pain in pit of the stomach seven months ago; it was worse after food, but it is only for the last month

that he has vomited his food, and this relieved his pain. He has never vomited blood; he has rapidly lost flesh.

On admission (9 January 1902) an indefinite mass moving with respiration can be felt to the left of the epigastric region. He only vomits occasionally and the pain is not constant or severe.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1902.										
Jan. 10.	4·14	9·7	70	·85	31·58	1·52	65·35	1·52	0	No red cell change.
Jan. 17.	4·12	6	68	·82	33·75	4·4	60·55	1·28	0	
Jan. 24.	3·40	4·7	60	·88	37·46	4·18	56·49	2·07	0	
Jan. 31.	3·09	8	60	·97	38·74	9·8	48·21	2·14	1·07	Achromic cells, poikilocytes, and polychromatophilic cells. He does not feel so well to-day. Went home for three weeks.
Mar. 10.	3·67	8·2	48	·65	31·16	1·53	65·07	·85	0	A few poikilocytes, else no change in cells.

Case XV. (Surgical Register 30, 1902).—Thomas M., aged 48. Has had pain and vomiting after taking food for the last four months; no hæmatemesis. Has lost three stone in weight.

On admission (4 January 1902) he is much emaciated, and has a peculiar yellow red complexion, which has been noticed for two weeks. There is an area of diminished resonance in the left hypochondriac region, and an indefinite tumour can be felt.

He died 14 January, ten days after admission. Unfortunately no post-mortem examination could be obtained.

Only one blood examination was made, and that on the day before death.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1902. Jan. 13.	3·62	24·57	42	·58	9·99	3·84	85·71	·4	0	Macrocytes, microcytes, poikilocytes, and achromic cells. No nucleated red cells.

Case XVI. (Medical Register 1394, 1901).—William C., aged 44. Twelve months ago he had a sudden attack of hæmatemesis, which, however, did not recur till six months later (May 1901), since when he has been losing flesh. For the last three months he has been unable to take solid food without vomiting.

On admission (31 December 1901) a small tumour, moving with respiration, can be felt above and to the left of the umbilicus; there is no tenderness on pressure. He is sick each

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1902. Jan. 10.	6·27	11·3	50	·4	18·96	2·39	77·34	1·28	0	Poikilocytes, microcytes, and achromic cells.
Jan. 17.	4·79	9·57	50	·52	17·6	3·4	78·6	·40	0	Ditto.
Jan. 24.	4·35	7	45	·51	15·7	6·5	77	·75	0	Ditto. Operation 25 Jan. 1902.
Jan. 31.	4·77	10·1	50	·52	14·2	1·64	83·02	1·1	0	Ditto.
Feb. 7.	3·75	10·2	48	·64	15·13	1·36	82·56	·91	0	Ditto.

day; the vomit is alkaline and consists of mucus mixed with some food; a bougie was arrested apparently at the cardiac orifice.

On 25 January 1902 laparotomy was performed. The stomach was fixed by a growth extending from the œsophagus along the whole extent of the lesser curvature to the pylorus; the œsophagus and left lobe of the liver were also involved in the same growth. He left the hospital unrelieved on 19 February 1902.

Sarcoma of the Ischio-rectal Fossa.

Case XVII. (Cancer Register 243, 1900).—Agnes H., aged 26. A hard swelling was noticed two and a half months ago in the left labium near the anus, to which was attributed

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Lymphocytes, Small and Large.	Large Mononuclear Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901. Jan. 17.	9·23	22	46·18	8·67	38·84	6·19	0	2 P.M.
Jan. 18.	7·47	14·25	35·88	0·96	59·29	3·84	0	11 A.M.
Jan. 26.	5·01	9·83	19·91	13·76	61·59	3·98	·72	11 A.M. Polymorphonuclear cells shew vacuoles.
Feb. 8.	4·83	9·6	31·74	9·18	57·77	1·26	0	2·30 P.M. No vacuolated cells seen.
Feb. 19.	4·96	13	29·67	11·29	57·59	1·06	·35	2 P.M. Most of the white cells, all varieties, shew vacuolation.
Feb. 21.	4·88	—	25·7	10·8	60·81	2·3	·35	Ditto.
Mar. 13.	—	—	20·82	7·94	69·31	1·51	·37	2 P.M. Ditto.
April 2.	5·69	12·16	24·72	5·28	68·02	1·41	·53	2 P.M. Ditto.
April 30.	4·7	12·14	18·83	3·33	76·58	·88	·35	3 P.M. Ditto. A few microcytes and poikilocytes.
May 31.	5·05	9	12·38	4·27	80·34	2·56	·42	3 P.M. Ditto. The polymorphonuclear cells are very granular and deeply oxyphil stained; a few red cells have larger diameters.

the continuous dragging pain which she has had for the last eight months; three months ago she gave birth to a child.

On admission (8 November 1900) there is a large, irregular, deep chasm, mainly on median aspect of right buttock, indicating where the growth had been incised before admission. The surface is covered with slough and foul discharge; there is induration in left buttock, which extends forwards into perineum and left labium majus.

On 12 December the growth was freely removed by an extensive operation. In the course of a few weeks, however, it recurred at the original site, also in inguinal glands, and later in both breasts and glands above clavicle. She died on 25 June 1901.

Post-mortem examination: There is a large mass of new growth on the left side of the perineum, springing from the ischio-rectal fossa. Inguinal, pelvic, and lumbar glands much enlarged by new growth. There is a large mass of cervical glands, also infiltrated by new growth.

Microscopic examination: The growth was a round-celled sarcoma.

Carcinoma of Rectum.

Case XVIII. (Cancer Register 297, 1901).—Catherine S., aged 59. Has had diarrhœa and abdominal pain and loss of flesh for the last nine months, especially during the last two months, with occasional loss of blood with the motions.

On admission (16 October 1900) the abdominal wall is resistant; there is tenderness in epigastrium; the liver is very

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901.								
Feb. 11.	5·3	11	8·09	4·84	86·3	·58	·14	
Feb. 14.	6·58	34	11·64	5·25	82·66	·13	·26	

enlarged. By rectal examination there is to be felt just above internal sphincter a hard, rough, irregular, ulcerated growth fixed to the surrounding tissues.

By 31 December the liver had attained a very large size, but there was no jaundice. She died 13 March 1901. Post-mortem examination shewed carcinoma of rectum with secondary growth in liver.

Microscopic examination: The growth was a columnar-celled carcinoma.

Carcinoma of Bowel.

Case XIX. (Surgical Register 5, 1902).—Mary Ann C., aged 52. Was admitted on 2 January 1902 for subacute intestinal obstruction, which was relieved by enemata and drugs, but epigastric pain continued. On 21 January laparotomy was performed, which exposed an extensive growth of the transverse colon. After a colotomy on 28 January she was discharged on 17 February.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1902. Feb. 6.	4·3	7·4	75	·87	35·41	3·23	57·14	3·42	·76	Macrocytes, microcytes, poikilocytes, and achromic cells; three normoblasts were counted to 525 white cells.
Feb. 13.	3·7	6	72	·97	28·79	7·48	60·85	2·25	·6	Ditto. No normoblasts were counted.

Carcinoma of Uterus.

Case XX. (Cancer Register 314, 1901).—Elizabeth R., aged 33. Two months ago she had severe hæmorrhage from the womb, lasting five days, which recurred three weeks later, there being no discharge between the attacks.

On admission (20 August 1900), by vaginal examination there is found a large growth all round the cervix, which is much ulcerated; the uterus is fixed; no infected glands to be observed. She died 14 April 1901.

At the post-mortem examination was found carcinoma of the cervix invading anterior wall of the body, also the vagina, bladder, right broad ligament, and both ovaries; there were secondary deposits in the lumbar glands.

Microscopic examination: The growth was a squamous-celled carcinoma.

It should be noted that between the dates of the first and last blood examination there was no hæmorrhage.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1900. Dec. 12.	3·2	14	14·5	8	67·5	11	0	2 P.M.
1901. Jan. 1.	2·2	6	22·2	5	54·4	18·4	0	„
Jan. 8.	2·01	7	17·3	6·08	70	6·52	0	„
Jan. 15.	3·95	24	21·92	4·54	70·32	3·2	0	„
Jan. 28.	3·57	13	13·25	7·42	78·09	·88	0	„

Case XXI. (Cancer Register 286, 1901).—Emily G., aged 39. For the last three months she has had excessive hæmorrhage at her periods, and a white discharge during the intervals; she has pain in right side and down the right leg, and has been losing flesh.

On admission (9 November 1900) the left side and anterior wall of the vagina are infiltrated and slightly ulcerated to within one and a half inches from the vulva. This infiltration is continuous with a hard mass in the cervix. The right broad ligament is involved and the uterus is fixed; posterior fornix

and right wall of the vagina are free from growth. Since admission the periods have been regular and given no trouble; the last was from 18 to 22 December. Up to three weeks before death the temperature stood at 100—100·2 degrees at night. About 20 January she was passing only very little urine, and this diminished down to three ounces on the day before death. Twelve days before she died she developed acute urticaria. She died with symptoms of uræmia on 17 February 1901.

On post-mortem examination was found carcinoma of cervix, involving anterior fornix, back of bladder, and roof of vagina; the body of the uterus was not affected. The left ovary was enlarged and contained a mass of new growth. There was advanced hydronephrosis of the right kidney.

Microscopic examination: The growth was a squamous-celled carcinoma.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901. Jan. 10.	3·7	25	18·73	7	66·1	7·9	0	2 P.M. Nineteen days after last period. Temp. = 100·2° F. last night.
Jan. 15.	2·89	14	17·82	6·19	72·76	3·87	0	2 P.M.
Jan. 21.	4·76	47·2	13·36	5·78	78·08	2·22	·22	2 P.M. Very little urine is being passed.
Jan. 29.	2·65	18·4	11·37	2·45	81·53	4	·61	2 P.M. She vomited twice this morning. Very little urine. Face puffy.

Case XXII. (Cancer Clinical Register 319, 1902).—Charlotte F., aged 37. She had severe metrorrhagia in June 1901. Later she suffered intermittent pain and has lost flesh.

On admission (13 February 1902) she seems to be well nourished and in fair health. On vaginal examination the

cervix is found indurated and ulcerated; the uterus is fixed there is induration of both broad ligaments, also slightly of anterior vaginal wall. There is no hæmorrhage or discharge, and pain is only occasional.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1902. Feb. 27.	4·30	7·5	·84	·97	22·11	3·18	72·55	1·7	·42	Slight irregularity of red cell diameter.
Mar. 6.	4·36	10	86	·98	26·93	1·78	70·01	1·07	·17	No red cell change.

Case XXIII. (Cancer Clinical Register 191, 1901).—Agnes T., aged 44. A swelling of the abdomen was first noticed in July 1900, and in the following November she underwent an operation in the Sussex County Hospital. A note from that Institution states: "A malignant ovarian cyst was removed, but unfortunately there were secondary growths in the peritoneum." She was relieved for two months, but had pain in the left side, and abdomen again swelled.

On admission (5 February 1901) the abdomen is much distended; there is dulness in the lower part up to the superior iliac spines on both sides; in addition there is dulness in the left flank and nearly up to middle line; on the right side this area is resonant. On vaginal examination the uterus is found to be a good deal fixed, and there is marked thickening in the left and anterior fornix.

She is tapped every seven to ten days. The largest amount of fluid drawn off was on 31 July = 432 ounces, but from this date it has decreased, and on 8 December it was only 274 ounces. She seems very well in herself, though keeps her bed; she has but little pain except when the abdomen is distended.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901. Feb. 25.	—	—	—	—	37·82	8·08	52·2	1·47	·36	Many white cells shew vacuolations.
Mar. 6.	—	—	—	—	33·72	8·86	56·11	1·43	0	Ditto.
Oct. 9.	4·39	23·5	—	—	24·12	8·99	65·66	1·18	·29	Ditto.
Oct. 16.	4·58	11·3	—	—	24·99	6·53	66·82	1·4	·23	Ditto. A few macrocytes.
Oct. 23.	4·86	12·8	91	·93	20·99	4·87	73·42	·69	0	
Oct. 30.	5·54	11·16	98	·89	21·47	7·02	69·72	1·56	·19	Polymorphonuclear cells are very granular, and some of them shew vacuolations.
Nov. 6.	4·9	13·8	95	·96	18·67	9·22	70·96	·57	·19	
Nov. 13.	4·87	15·4	—	—	23·06	5·82	69·49	·79	·79	A few poikilocytes; leucocytes granular and vacuolated.
Nov. 20.	4·08	16	—	—	25·56	3·11	69·73	·69	·86	Ditto.
Nov. 27.	4·09	10·5	—	—	22·75	5·43	70·42	·58	·77	
1902. Mar. 3.	4·92	12·7	97	·98	13·37	2·11	83·44	·92	·13	Many white cells and vacuolated red cells, good colour; a few macrocytes, microcytes, and poikilocytes, and many polychromatophilic cells.

Case XXIV. (Cancer Register 160, 1900).—Elizabeth T., aged 68. Five years ago (1895) she first noticed a small, hard, tender swelling in the right side of the vulva. It increased in size and became painful, and in 1896 it was removed by operation. Two years later it recurred at the original site.

On admission (5 August 1900) there is, protruding between

the labia, an excoriated mass about the size of an orange, occluding the entrance to the vagina. It involves both labia and extends practically down to the bone on the left side. It involves chiefly the præurethral tissues, extending up the vagina for an inch and a half. The cervix appears healthy and no glands can be felt in the pelvis.

On 14 August the growth was freely removed, since when she has remained in perfectly good health, excepting slight bronchial attacks. On 22 February 1902 she died, after a few days' illness from acute bronchitis.

Post-mortem shewed an entire absence in any part of the body of any new growth.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1900. Dec. 31.	6·02	14	—	—	33·5	4·5	51·5	10·5	0	2 P.M.
1901. Jan. 8.	6·7	11	—	—	27·11	8·4	55·4	9·6	0	„
Jan. 24.	4·87	15	—	—	32·77	4·08	58·4	3	1·63	„
Mar. 29.	6·7	16·8	—	—	33·19	5·9	58·39	2·29	·19	„
Oct. 7.	6·3	10	—	—	38·75	2·93	54·21	3·66	·36	Noon.
Oct. 14.	4·9	6·7	—	—	34·3	11·41	49·72	3·32	1·1	11 A.M.
Oct. 21.	5·17	8	105	1·01	43·25	2·6	51·51	2·41	·2	„
Oct. 28.	5·78	6·23	—	—	37·09	9·66	50	2·41	·8	
Nov. 4.	5·39	7·3	—	—	35·32	10·57	52·4	·96	·72	
Nov. 11.	4·95	7·6	—	—	37·43	4·67	56·59	·85	·42	
Nov. 18.	5·08	9	102	1	34·75	3·94	59·71	1·1	·47	
Nov. 25.	4·38	8·6	92	1·05	29·65	5·91	61·67	1·84	·78	
Dec. 2.	4·56	9·9	90	·98	31·29	5·93	57·72	4·06	·94	No red cell change.

Microscopic examination: The growth removed was a squamous-celled carcinoma.

Note that the first four counts were made about one hour after the patient's dinner. The increase of white cells is probably a digestion leucocytosis.

Carcinoma of Tongue.

CASE XXV. (Cancer Register 425, 1901).—Henry F., aged 60. He first noticed a spot on the left side of his tongue eight months ago (December 1900); four months later he noticed a swelling in left side of the neck.

On admission (10 August 1901) he is much emaciated. There is an irregularly defined growth on the left side of the tongue, extending from midway between the tip and the base to the anterior pillar of the fauces, which is also involved. The growth is hard and raised, and from its centre springs a pedunculated mass about the size of a bean; there is no ulceration. Below and in front of the angle of the left jaw are three enlarged glands the size of a pigeon's egg; there is much salivation; has a cough, and the temperature usually raised at night—101° F. to 102° F.; he can take his food fairly well. He died 28 October 1901.

The post-mortem examination shewed, in addition to the new growth, an empyema of right chest and pyopericarditis—ten ounces of purulent fluid in pericardium.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901.										
Oct. 11.	3·9	24	—	—	26·7	2·8	69·29	1·2	0	
Oct. 18.	3·32	20·4	—	—	12·04	3·96	83·57	·26	·13	Irregular diameter of red cell. White cells with vacuolations.
Oct. 25.	4·12	11·5	80	·97	24·69	3·3	71·98	0	0	

Microscopic examination: The growth was a squamous-celled carcinoma.

Carcinoma of Larynx.

CASE XXVI. (Cancer Register 464, 1901).—Frederick D., aged 39. The disease was first noticed twelve months ago (November 1900), since when he has been losing flesh, and for the last six months has been unable to take solid food.

On admission (23 November 1901) there is advanced ulceration of larynx, extending to the root of the tongue. He died 11 December 1901.

Post-mortem examination: Mass of new growth involving posterior third of tongue, and extending back to the larynx and destroying the epiglottis; sub-maxillary glands infiltrated with new growth; septic pneumonia.

Microscopic examination: The growth was a squamous-celled carcinoma.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901. Dec. 6.	2·47	6·3	25·83	4·49	69·93	·16	·16	

Melanotic Sarcoma.

CASE XXVII. (Cancer Register 474, 1901).—August H., aged 66. Five years ago he had a malignant growth, said to be epitheliomatous, removed from his left heel. It recurred after some years in the left inguinal glands.

On admission (23 May 1901) there is a large red nodular mass about ten inches in diameter and projecting about five inches, involving the whole of Scarpa's triangle on the left side. The surface is smooth, with deep fissures between the nodules,

which are hard and firmly attached to the underlying structures. At this date he had but little pain.

In November the pain was constant, the growth commenced to ulcerate, and from these surfaces there was on several occasions severe hæmorrhage, which greatly weakened him, and he died 21 December 1901.

At the post-mortem examination the growth is seen on section to be in some parts broken down or caseous, and in others pigmented. The right suprarenal body is replaced by a globular mass of growth 1¼ inches in diameter, which is also pigmented.

Microscopic examination: The growth was a melanotic round-celled sarcoma.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901.										
Oct. 7.	3·82	8·4	—	—	13·48	5·85	78·59	1·46	·58	
Oct. 14.	3·86	6·29	—	—	21 9	4·06	72·83	·84	·33	
Oct. 21.	4·06	10·09	75	·92	19·73	4·04	75·55	·59	0	
Oct. 28.	4·3	5·8	—	—	36·83	6·32	55·46	·81	·54	A few macrocytes and microcytes.
Nov. 4.	4·1	13·29	—	—	9·6	4·33	85·89	·15	0	A few macrocytes, microcytes, and poikilocytes.

Sarcoma of Tibia.

Case XXVIII. (Cancer Register 327, 1901).—Florence M., aged 37. She has had a painful swelling on the outer side of her left tibia since 1893, and she had submitted on several occasions to operations, at which the tumour was partially removed or incised.

On admission (30 April 1901) there is a nodular tumour of the head of the tibia. It projects about two inches from the bony surface and extends a little beyond the tubercle. It is of unequal consistency, hard and soft, and even fluctuating in places, and very painful. On 2 June the leg was amputated above the knee, and she was discharged convalescent on 22 June.

The single blood examination was made a few hours previous to the operation.

Microscopic examination: The growth was a sarcoma, which had undergone extensive myxomatous change.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901. June 2.	5·08	8·5	29·61	6·37	62·41	1·59	0	

Sarcoma of Femur.

Case XXIX. (Cancer Clinical Register 255, 1901).—Emily P., aged 28. Seven years ago the right leg was amputated at middle third of femur for sarcomatous disease. She remained quite well until two years ago, when she noticed a swelling of the left knee.

On admission (8 July 1901) there is a painful swelling of the left knee extending up a third of the femur. There are two growths on the tibia, the limb being quite immovable. The stump of the right thigh is greatly enlarged, and there are hard enlarged glands in both groins. Her condition varies from day to day, and is apparently dependent on the amount of pain, which prevents sleep; on the whole she remains about the same.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901.										
Oct. 30.	4·05	13	—	—	19·72	6·78	68·02	3·74	1·7	
Nov. 6.	3·55	9	70	·98	31	4·1	63·7	·72	·36	
Nov. 13.	3·45	8·3	65	·94	21·33	5·92	70·12	1·66	·92	A few microcytes and macrocytes.
Nov. 20.	3·23	8	65	1	23·2	3·83	71·37	·96	·58	Ditto.
Nov. 27.	3·69	8·3	60	·81	26·49	1·26	71·5	·18	·54	
Dec. 4.	3·34	8·85	65	·97	27·65	3·05	68·48	·48	·32	
Dec. 11.	4·08	9·7	75	·91	16·1	7·15	74·66	1·5	·5	Increased pain since last week; she seems very ill.
Dec. 18.	3·77	9·25	60	·79	24·14	5·16	68·96	1·53	·19	Much better again. Many microcytes.
1902.										
Jan. 1.	3·19	10·5	55	·86	26	4·87	66·66	1·55	·88	
Jan. 8.	3·34	8·16	60	·88	26·49	4·84	67·16	1·49	0	
Jan. 15.	3·15	6·71	65	1·03	18·67	1·02	77·85	1·9	·51	Has been very ill again; is now drowsy from morphia.
Jan. 22.	3·06	7	60	·98	26·2	3·9	67	1·6	1	Variable diameter of red cells; a few poikilocytes.
Jan. 29.	3·36	7	65	·96	20·56	6·55	72·21	·21	·43	
Feb. 5.	3·06	8·14	65	1·05	23·16	3·2	70·81	2·14	·64	A few poikilocytes, microcytes, and achromic cells.

Round-celled Sarcoma.

Case XXX. (Cancer Clinical Register 251, 1901).—David J., aged 38. A swelling first appeared on the left side of neck below the ramus of jaw eight years ago, in 1893; it increased

rapidly, gave great pain, and in November 1900 he was admitted and the tumour excised. Microscopic section shewed "small round-celled sarcoma." It slowly recurred, and he was readmitted 27 July 1901. There is a diffuse swelling from left angle of jaw backwards to anterior border of the trapezius, and down to within two inches of the clavicle. On right side there is a swelling between angle of jaw and sterno-mastoid; operation is not advisable. He has remained in much the same condition, and pain is not constant or severe. In January 1902 treatment by X-Rays was started three and four times a week for ten minutes at a time. At the date of the last blood examination there did not appear to have been any definite improvement.

Date.	Red Cells in Millions per c.mm.	White Cells in Thousands per c.mm.	Hb. p.c.	Hb. Index.	Lymphocytes, Small and Large.	Large Mononuclear Hyaline Cells.	Polymorphonuclear Cells.	Eosinophil Cells.	Mast Cells.	Remarks.
1901.										
Oct. 4.	5·61	14	—	—	19·12	2·16	78·08	·61	0	
Oct. 11.	5·26	16·57	—	—	18·04	4·27	75·4	2	·26	
Oct. 18.	5·21	17	94	·9	14·74	3·82	79·88	1·34	·19	Red Cells of varying diameter and uneven staining, but no marked changes at any examination.
Oct. 25.	5·06	16·85	—	—	15·94	8·18	75·53	·7	·7	
Nov. 1.	5·01	17·28	90	·9	12·34	7·54	78·08	·25	·75	
Nov. 8.	5·04	15·3	—	—	16·42	4·92	75·58	1·87	1·17	
Dec. 6.	5·59	31·37	95	·86	14·83	7·32	74·66	2·33	·83	
1902.										
Feb. 10.	5·47	14·5	100	·92	19·1	4·6	76·03	·23	0	

VIII.

Conclusions.

On reviewing the reports of the examinations given above, it will be seen that the results of the cytologic analysis of the blood in these thirty cases of malignant disease are very variable, and that in no one case can any single examination be found to shew any special characteristic that can be regarded as specific or of the slightest diagnostic value; but on observing the results of the analyses in those cases where several examinations were made, it may be noted that in a great number of examples the progressive series have a tendency to conform to a more or less marked type, which is in part well shewn in the accompanying charts. It is, however, in no way claimed that the type is specific or peculiar to cancer, since the number of observations are too limited to form definite conclusions, and the knowledge of comparative series in other diseases is as yet small, although it may be allowed that in its general bearing it is quite in accordance with the opinions arrived at by most of the workers in this subject.

The most prominent feature of this type, or serial principle, is a gradual increase in percentage of polymorphonuclear cells, associated with a corresponding diminution of lymphocytes; in other words, a gradual increase of granular leucocytes at the expense of the non-granular, and this quite independently of the presence or not of leucocytosis.

Thus, of the sixteen fatal cases eleven shewed a markedly raised percentage of polymorphonuclear cells at the last count; of the five cases in which this was not observed, two (Cases IX. and XXIV.) died from bronchial attacks having no connection with the progress of the cancerous disease—indeed, XXIV. shewed at the autopsy no sign whatever of malignant disease. Two other cases were carcinoma of stomach, where in both the disease was virtually limited to that organ, and had only formed few secondary deposits, the fifth case (XXVI.) being the only disease of the larynx examined. Of the fourteen non-fatal cases seven shewed a more or less raised percentage of polymorphonuclear cells as the case progressed; and of the seven remaining cases where the condition was not observed,

three were operation cases (XIII., XIX., XXVIII.), one (XIV.) is a stomach case, and the remainder (VI., VIII., XXII.) are patients in comparatively very good health.

The writer would like to draw attention to these three cases of cancer of the stomach, two of which shewed at the autopsy only small development of metastases, and to refer to the four other gastric cases in which the increased percentage of polymorphonuclear cells was observed. In two of these cases it was shewn at the operation that there were extensive secondary deposits in the liver or peritoneal glands, and of the two others—one fatal (no post-mortem) and the other still progressing—the patients bore a marked yellow tint suggestive of liver complications. Of course the number of cases is far too small to form generalization, but nevertheless the facts appear very interesting.

In the above cases it is remarkable that leucocytosis is only a comparatively rare occurrence, and not of extreme degree in any case, and is moreover not a constant symptom, the leucocytes being raised in number one week, but being within physiological limits at the next count a week later.

A second feature, which also is not by any means a constant one, but which occurs in a sufficient number of examinations to make it notable, is the increased percentage over the now accepted normal of the large mononuclear hyaline cells. A large proportion of this group is composed of the so-called transitional cells, which in many of the above cases presented very remarkable forms, some of which are represented in Fig. 1, Plate IV. If these cells are really to be regarded as transitional cells—that is, cells which are passing from the condition of a non-granular mononuclear cell to that of a granular polymorphonuclear cell—this second feature may be regarded as quite supporting the first feature.

As a rule, and quite in agreement with the observations of others, the number of red cells and the hæmoglobin are diminished in cachectic cases, and where there has been rapid or great loss of flesh—and even in those cases where, owing to lack of nourishment, vomiting, or diarrhœa, the blood has become more concentrated and the red cell count correspondingly raised—the hæmoglobin index or corpuscular value is lowered; and this colour index shews a progressive gradual lowering with

the progress of the case. On the other hand, this also is a most inconstant symptom, as in many cases the colour index may at the last count remain as it was or even higher than at the first count. And several cases just before death shew a hæmoglobin index not greatly lowered from the normal. In some instances the colour index has been over unity, but this was never associated with any other symptom of pernicious anæmia.

A fourth, and perhaps the most constant feature, is the notable presence of poikilocytosis and variability of red cell diameter, a condition which in many cases is observed in quite early stages, where red cell count and hæmoglobin index and leucocyte percentage hardly vary from the normal. This feature becomes progressively accentuated, and in some cases of extreme character, towards the fatal termination.

The relations of the percentages of eosinophil cells and of mast cells, also of nucleated red cells, to the blood of cancerous patients is, from the above cases, not very apparent, but it is hoped that these and the question of the conclusions suggested by this short research may be dealt with in a more extensive manner in a future Paper.

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DESCRIPTION OF PLATES III. AND IV.

(See pages 140—143.)

PLATE III.

FIG. 1.—(*a*) Normal red cells.
(*b*) Macrocytes.
(*c*) and (*d*) Achromic cells.
(*e*) Polychromatophilic cells.
(*f*) Poikilocytes.
(*g*) Microcytes.

FIG. 2.—(*a*) Normal red cells.
(*b*) Normoblasts (division of nucleus shewn in two).
(*c*) Normoblast with nucleus (?) being discharged from the cell.
(*d*) Poikiloblast.
(*e*) Megaloblast.
(*f*) "Diplococcus-like" bodies.
(*g*) "Yeast-like" bodies.

FIG. 3.—Small and large lymphocytes.

FIG. 4.—Large mononuclear hyaline cells—two show vacuolation.

PLATE IV.

FIG. 1.—So-called transitional cells, shewing the two varieties mentioned in text.

FIG. 2.—Polymorphonuclear leucocytes. These are depicted rather more oxyphil than is commonly the case. The protoplasm is usually less or more finely granular than is here shewn. Vacuolation is shewn in two cells.

FIG. 3.—Eosinophil cells.

FIG. 4.—Mast cells.

DESCRIPTION OF CHARTS ON PLATE V.

The upper black curve represents the percentage number of granular leucocytes at successive blood examinations.

The lower black curve represents the percentage number of hyaline leucocytes at successive examinations.

The red curve represents the actual number in millions of red cells per cubic millimetre at successive examinations.

The blue curve represents the actual number of leucocytes in thousands per cubic millimetre at successive examinations.

PLATE III.

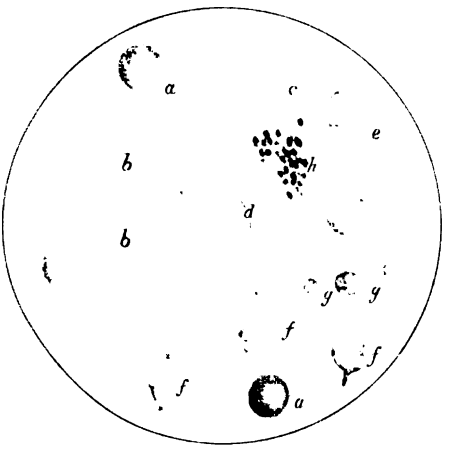


Fig. 1.

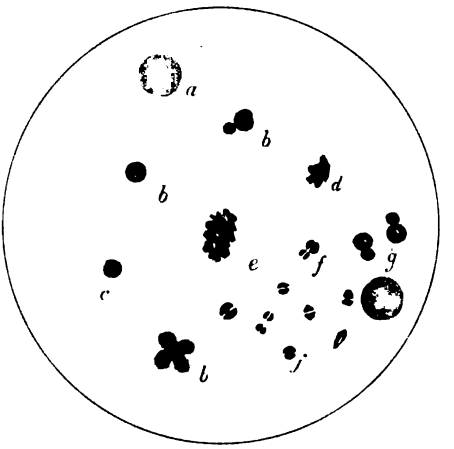


Fig. 2.

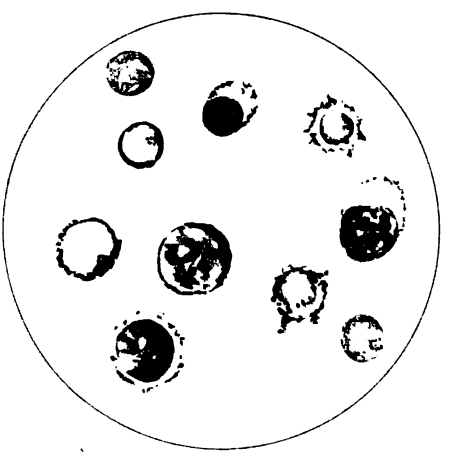


Fig. 3.

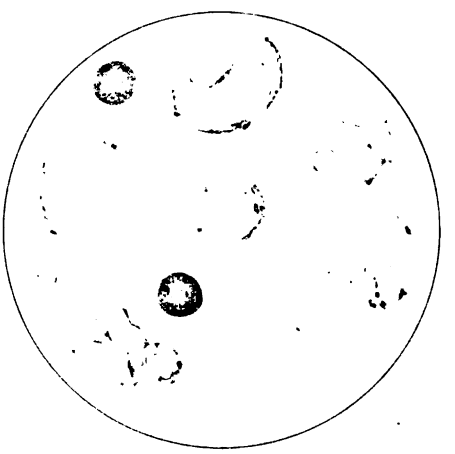


Fig. 4.

Bale & Danielsson, Ltd., Chromo-Lith.

PLATE IV.

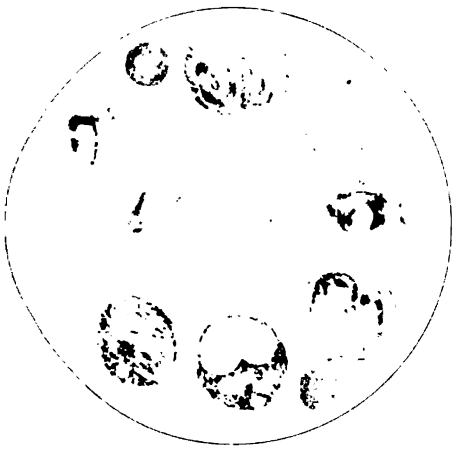


Fig. 1.

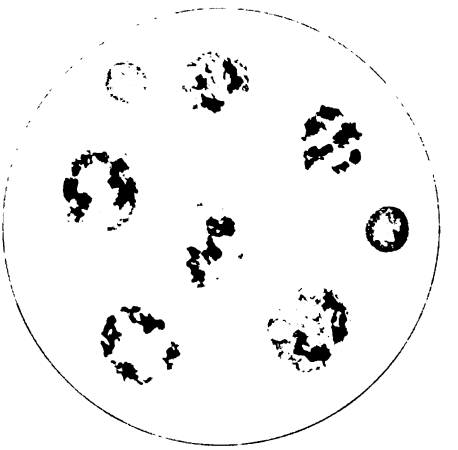


Fig. 2.

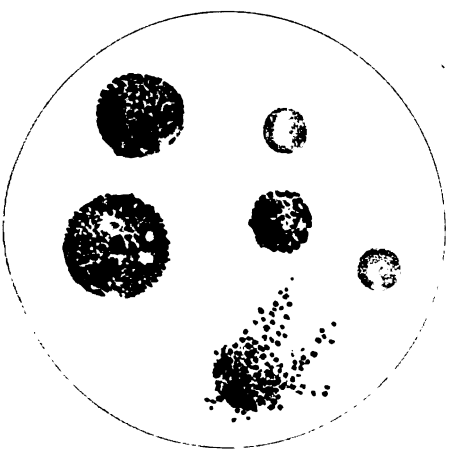


Fig. 3.

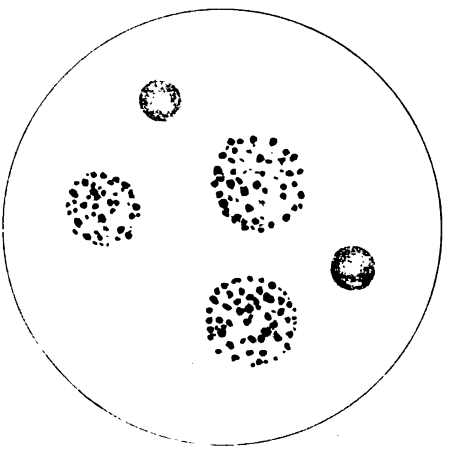
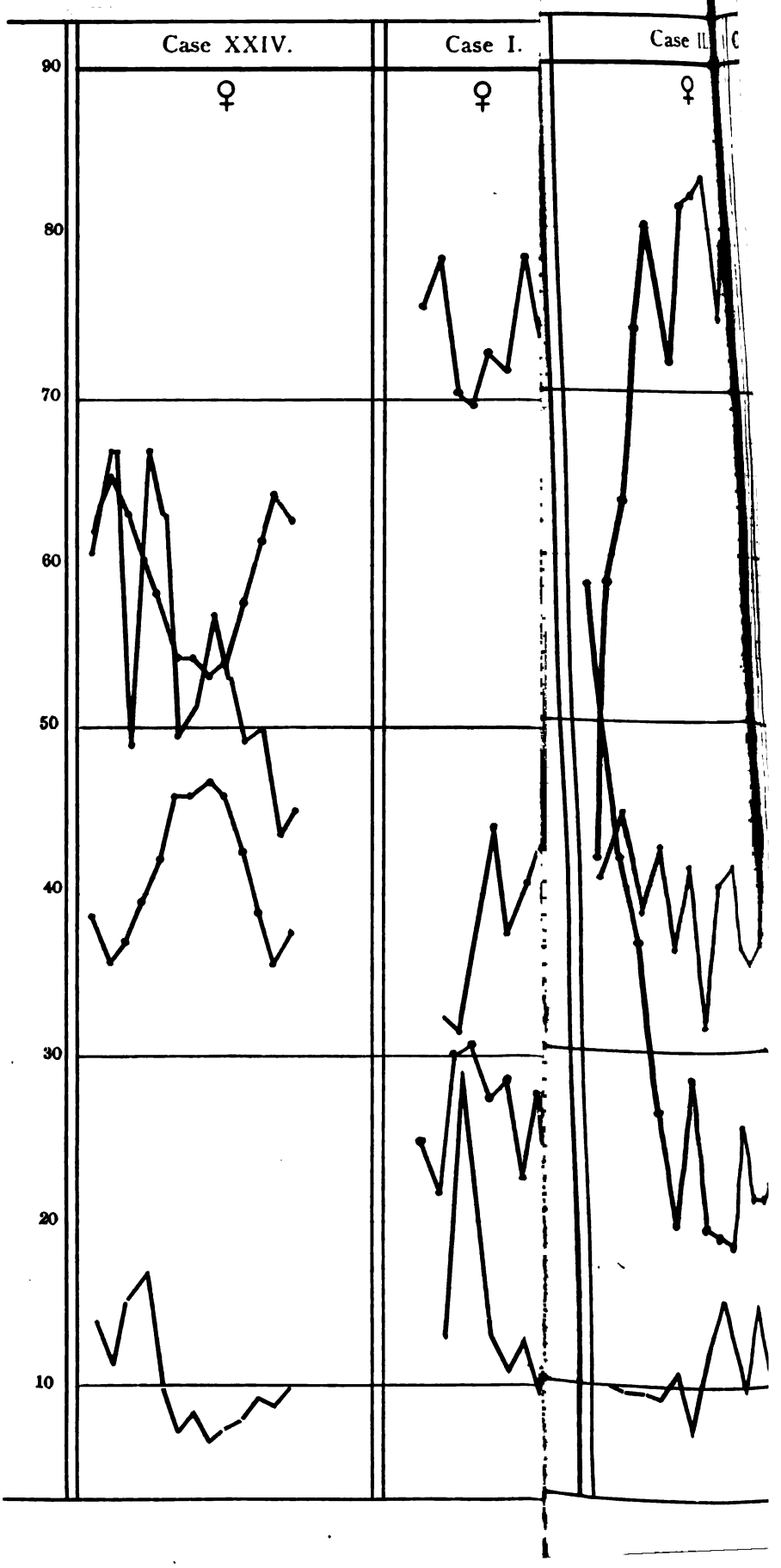
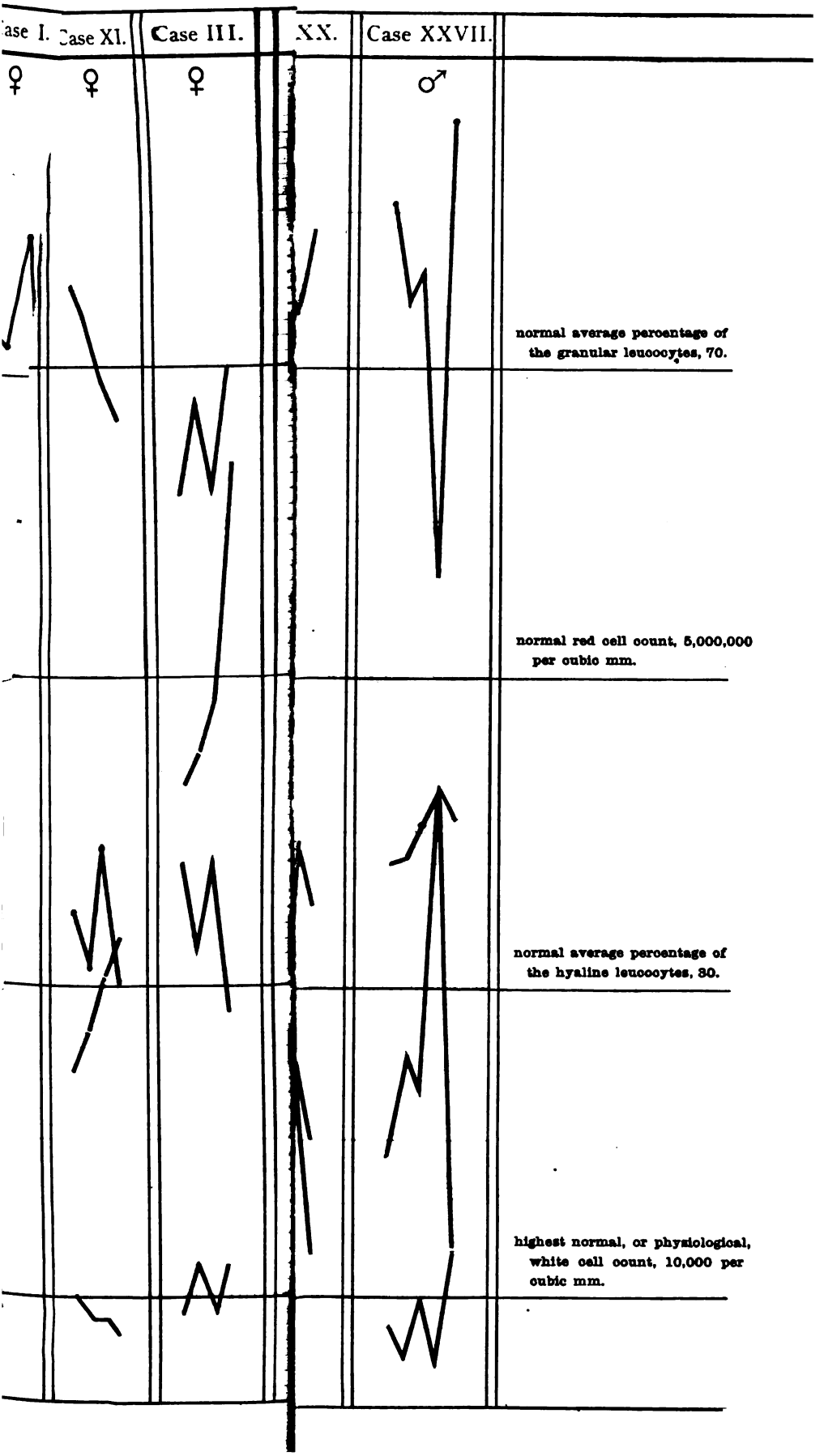


Fig. 4.

Bale & Danielsson, Ltd., Chromo-Lith.


Case XXIV.
Case I.
Case II.
♀
♀
♀
90
80
70
60
50
40
30
20
10


ase I.
Case XI.
Case III.
XX.
Case XXVII.
♀
♀
♀
♂
normal average percentage of the granular leucocytes, 70.
normal red cell count, 5,000,000 per cubic mm.
normal average percentage of the hyaline leucocytes, 30.
highest normal, or physiological, white cell count, 10,000 per cubic mm.

SOME STATISTICS RELATING TO 500 CASES OF MALIGNANT DISEASE.

By W. T. HILLIER,

PATHOLOGICAL ASSISTANT IN THE CANCER RESEARCH LABORATORIES.

THE material on which these statistics are founded represents 500 cases of malignant disease, which were admitted into The Middlesex Hospital during the 114 weeks between 1 January 1900 and 12 March 1902. Except that it was not possible, for one reason or another, to examine the material from several cases, and that in four other cases it was not found possible by microscopic examination to determine precisely the nature of new growths which clinically shewed every sign of malignancy, these 500 cases were exactly consecutive, and included every case of malignant disease admitted into the general wards of The Middlesex Hospital or into the cancer block during the period in question, and on which an operation was performed, or which was examined after death.

Before applying these statistics to malignant disease generally, there are certain limitations attaching to them which it will be well to refer to. In the first place there is a relatively large number of post-mortem examinations as compared with what would be the case in other London hospitals, for the reason that most of the patients admitted into the special cancer block are kept there until death.

Then, the statistics do not shew the true comparative prevalence of malignant disease in the two sexes, since the special cancer block provides forty beds for inoperable cases in women, whilst the special cancer ward for men provides accommodation for only nine such cases.

Similarly, the relative frequency of carcinoma and sarcoma shewn here is not that which holds good for these diseases

generally. Amongst the "hospital" class of patients, children are frequently taken to special children's hospitals, and so the average numerical frequency of sarcoma cases, as compared with those of carcinoma in general hospitals, is below the normal. At The Middlesex Hospital the balance between the two forms of malignant disease is further disturbed by the fact that practically only adults are admitted to the forty-nine beds of the special cancer establishment, and so cases of carcinoma again tend to predominate unduly over cases of sarcoma in the statistical returns.

The 500 cases of malignant disease were, by the results of microscopic examination, classified as: carcinoma 419 cases, and sarcoma 81 cases.

The 419 cases of carcinoma include eight cases of that form of carcinoma of the skin which is known clinically as "rodent ulcer."

As regards the material from these 500 cases, it was obtained from 253 cases which were operated on, and from 270 post-mortem examinations; twenty-three of the cases which were operated on subsequently died in the general wards of the Hospital or in the cancer block, and were examined post-mortem.

Cases with recurrence of malignant disease, having been previously treated in the Hospital, are only counted once in the returns.

The tables, which shew the relative frequency of secondary growths in different parts, are constructed solely from cases in which a post-mortem examination has been made. Further, in these tables only positive evidence is to be relied on. For instance, if at the post-mortem examination it was found that only the set of lymphatic glands next to the primary seat of new growth were affected, and none of the viscera or lymphatics elsewhere, an examination of the brain and bones was sometimes omitted. The thoracic and abdominal viscera have, of course, been thoroughly examined in every case except in one, when only a limited examination could be made.

In the tables no attempt is made when referring to paired or multiple organs, or parts, to indicate which one, or which set, were affected, as in the case of the kidneys, the bones, and the like.

In three cases there appeared to have been two distinct primary foci of malignant new growth in parts of the body remote from one another; and in classifying these three cases, what appeared to be the primary growth of older origin has alone been regarded for the purposes of the tables.

Thus, in two of the cases of carcinoma of the breast, there was what appeared to be an independent malignant new growth in the vagina, having no relation to the other new growth; and in one case of carcinoma of the tongue in a man there was what again appeared to be a new growth of independent origin in the kidney.

The age and sex incidence in the 500 cases was as follows:—

TABLE I.

CASES OF CARCINOMA TABULATED ACCORDING TO AGE AND SEX.

Situation of Primary New Growth.	15 to 20	20 to 25	25 to 30	30 to 35	35 to 40	40 to 45	45 to 50	50 to 55	55 to 60	60 to 65	65 to 70	70 to 75	75 to 80	80 to 85	85 to 90	M.	F.	Total.
Lip	..	..	..	..	1	1	3	1	1	2	2	..	..	1	..	12	..	12
Cheek	..	..	..	..	..	..	1	..	1	..	..	1	1	..	..	4	..	4
Palate	..	..	..	..	..	..	1	..	2	..	1	..	..	..	..	4	..	4
Tongue	..	..	..	1	1	3	7	7	13	5	2	1	1	..	..	41	..	47
	..	..	1	..	..	1	1	1	..	2	..	..	..	..	..	..	6	
Œsophagus	..	..	..	..	..	1	..	4	1	2	..	..	..	..	..	8	..	8
Stomach	..	..	..	..	1	1	..	3	4	2	1	..	..	..	..	12	..	19
	1	..	..	1	..	..	2	..	1	1	1	..	..	..	..	..	7	
Colon	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	1	..	7
	..	..	..	..	1	1	..	..	3	..	..	1	..	..	..	..	6	
Rectum	..	..	..	2	..	..	2	3	..	1	4	1	..	1	..	14	..	39
	..	..	..	..	1	4	4	4	4	1	4	1	1	1	..	..	25	
Omentum	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	1	..	1
Liver	..	..	..	..	1	..	..	1	1	..	..	..	..	..	..	3	..	4
	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	1	
Bile Duct	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	1	..	2
	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	1	
Pancreas	..	..	..	..	2	..	..	1	1	2	..	..	..	..	..	6	..	9
	..	..	2	..	1	..	..	..	..	..	..	..	..	..	..	..	3	
Kidney	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	1	..	2
	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	1	
Bladder	..	..	1	..	..	..	..	2	..	..	1	..	..	1	..	5	..	11
	..	..	..	..	..	1	1	..	..	2	1	..	1	..	..	..	6	
Vulva	..	..	..	..	..	1	..	2	..	..	1	1	..	..	..	..	5	5

Situation of Primary New Growth.	15 to 20	20 to 25	25 to 30	30 to 35	35 to 40	40 to 45	45 to 50	50 to 55	55 to 60	60 to 65	65 to 70	70 to 75	75 to 80	80 to 85	85 to 90	M.	F.	Total
Uterus	..	..	..	7	6	9	20	12	7	6	3	2	1	..	..	..	73	73
Prostate	..	..	..	..	..	..	..	..	..	..	2	1	..	..	..	3	..	3
Penis	..	..	..	..	1	2	..	1	..	..	..	2	..	..	..	6	..	6
Testicle	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	1	..	1
Scrotum	..	..	..	..	..	..	..	1	1	..	..	..	..	..	..	2	..	2
Skin, Trunk and Limbs	..	..	..	..	..	..	1	..	1	..	..	..	..	..	..	..	2	2
Skin, Scalp and Face	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	1	..	4
	..	..	..	..	..	..	1	..	..	1	1	..	..	..	..	..	3	
Skin, Nose	..	..	..	..	..	1	1	..	..	..	..	..	..	..	..	2	..	2
Skin, Rodent Ulcer	..	..	..	..	1	2	1	..	..	..	1	..	..	..	..	5	..	8
	..	..	..	..	..	..	..	1	1	..	1	..	..	..	..	..	3	
Breast	..	..	..	..	..	..	1	..	..	1	..	..	..	..	1	3	..	134
	..	..	1	6	13	14	23	21	26	18	7	2	..	..	..	..	131	
Parotid Gland	..	..	..	1	..	..	..	..	1	..	..	..	..	..	..	..	2	2
Maxilla	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	1	..	2
	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	1	
Larynx	..	..	..	..	1	..	..	..	..	2	..	..	..	..	..	3	..	5
	..	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	2	
Bronchus	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	1	1
Males	..	..	2	3	9	11	18	24	28	18	14	7	2	3	1	140		
Females	1	..	4	16	23	31	54	41	46	33	19	7	3	1	..		279	
Both Sexes	1	..	6	19	32	42	72	65	74	51	33	14	5	4	1			419

TABLE II.

CASES OF SARCOMA TABULATED ACCORDING TO AGE AND SEX.

Situation of Primary New Growth.	5 to 10	10 to 15	15 to 20	20 to 25	25 to 30	30 to 35	35 to 40	40 to 45	45 to 50	50 to 55	55 to 60	60 to 65	65 to 70	70 to 75	75 to 80	80 to 85	M.	F.	Total.
Skin and Subcutaneous Tissue	..	..	..	..	..	..	..	1	..	..	1	..	1	..	..	..	3	..	8
	..	..	..	..	..	..	1	1	..	..	1	1	1	..	..	..	..	5	
Bones:—Maxilla	1	1	..	..	..	..	1	..	..	..	..	..	1	1	..	..	5	..	6
	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	1	

Situation of Primary New Growth.	5 to 10	10 to 15	15 to 20	20 to 25	25 to 30	30 to 35	35 to 40	40 to 45	45 to 50	50 to 55	55 to 60	60 to 65	65 to 70	70 to 75	75 to 80	80 to 85	M.	F.	Total.
Bones:—Palate	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	1	1
Mandible	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	1	2	..	5
	..	..	1	1	..	..	..	1	..	..	..	..	..	..	..	..	..	3	
Humerus	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1
Innominate	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	2	..	4
	..	..	..	..	..	..	2	..	..	..	..	..	..	..	..	..	..	2	
Femur	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	6
	..	..	2	..	..	1	1	..	..	..	1	..	..	..	..	..	..	5	
Tibia	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	1	..	3
	..	..	..	..	..	..	1	..	..	1	..	..	..	..	..	..	..	2	
Fibula	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1
Muscles:—Deltoid	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	1	..	2
	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	1	
Pectoralis Major	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	1	1
Rectus Abdominis	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1
Rectus Femoris	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	1	1
Ischiō Rectal Fossa	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	1	1
Omentum	..	..	..	..	..	1	..	..	1	..	..	..	..	..	..	..	2	..	2
Retropharyngeal Tissue	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	1	1
Lymphatic Glands	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	1	..	5
	..	..	1	..	..	1	..	..	1	..	1	..	..	..	..	..	..	4	
Dura Mater	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	1	..	1
Stomach	..	..	..	..	..	..	..	1	..	..	..	1	..	..	..	..	2	..	2
Rectum	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	1	..	2
	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	1	
Kidney	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	1	..	2
	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	1	
Bladder	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	1	..	2
	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	1	
Ovary	..	..	1	..	..	..	..	1	..	..	..	..	..	..	..	..	..	2	2
Uterus	..	..	..	..	..	..	..	..	1	3	..	..	..	..	..	..	..	4	4
Vagina	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	1	1
Breast	..	..	..	..	..	..	1	4	4	1	1	1	..	1	..	..	..	13	13
Brain	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	2
	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	1	
Pleura	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	1	1
Males	1	2	2	1	..	2	1	2	2	1	2	4	2	1	..	1	24		
Females	1	2	5	2	1	3	6	10	8	6	5	4	1	3	..	..		57	
Both Sexes	2	4	7	3	1	5	7	12	10	7	7	8	3	4	..	1			81

PLATE VI. represents diagrammatically the relative frequency with which various parts and organs were primarily affected.

PLATES VII. and VIII. shew the relative frequency with which various organs and parts become secondarily affected, arranged according to the seat of primary disease.

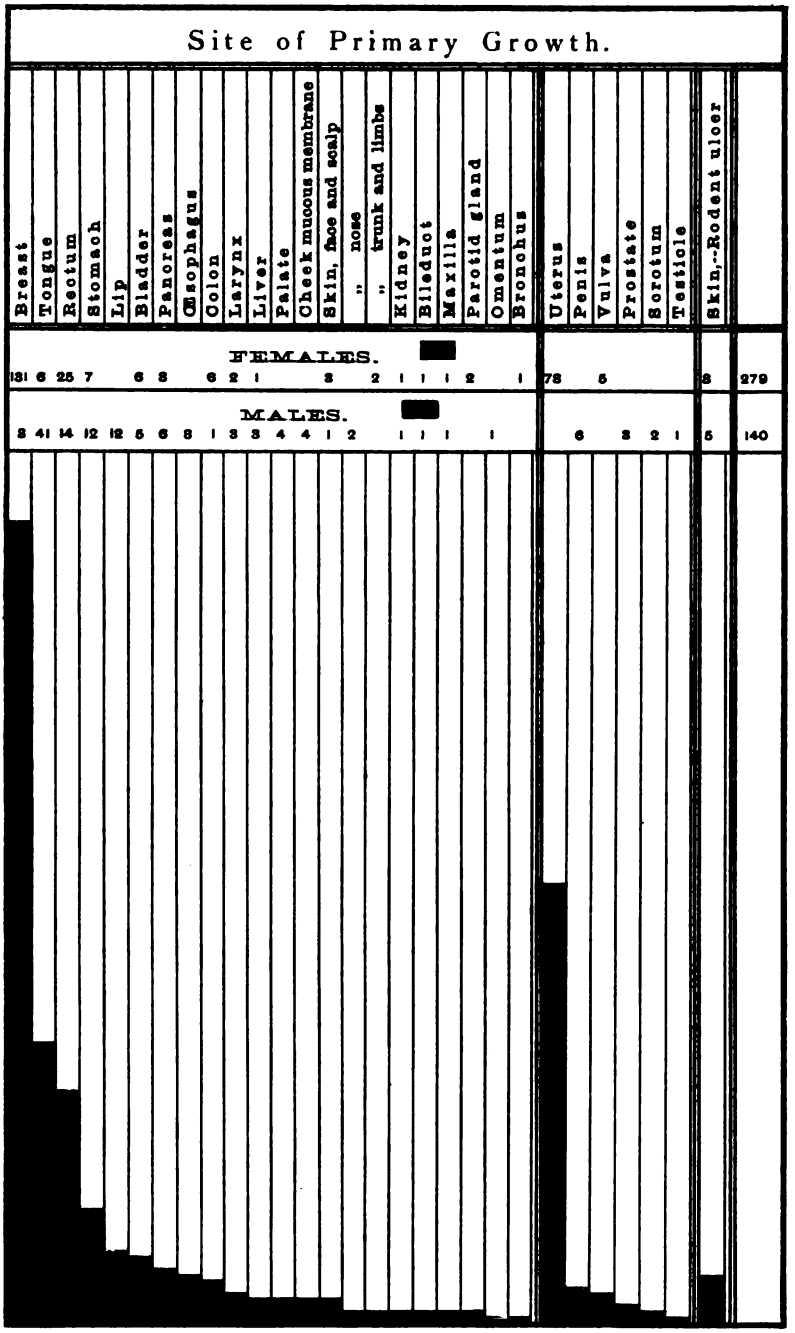
In sixty-one out of 240 cases which died with carcinoma no secondary new growth was found at the post-mortem examination:—

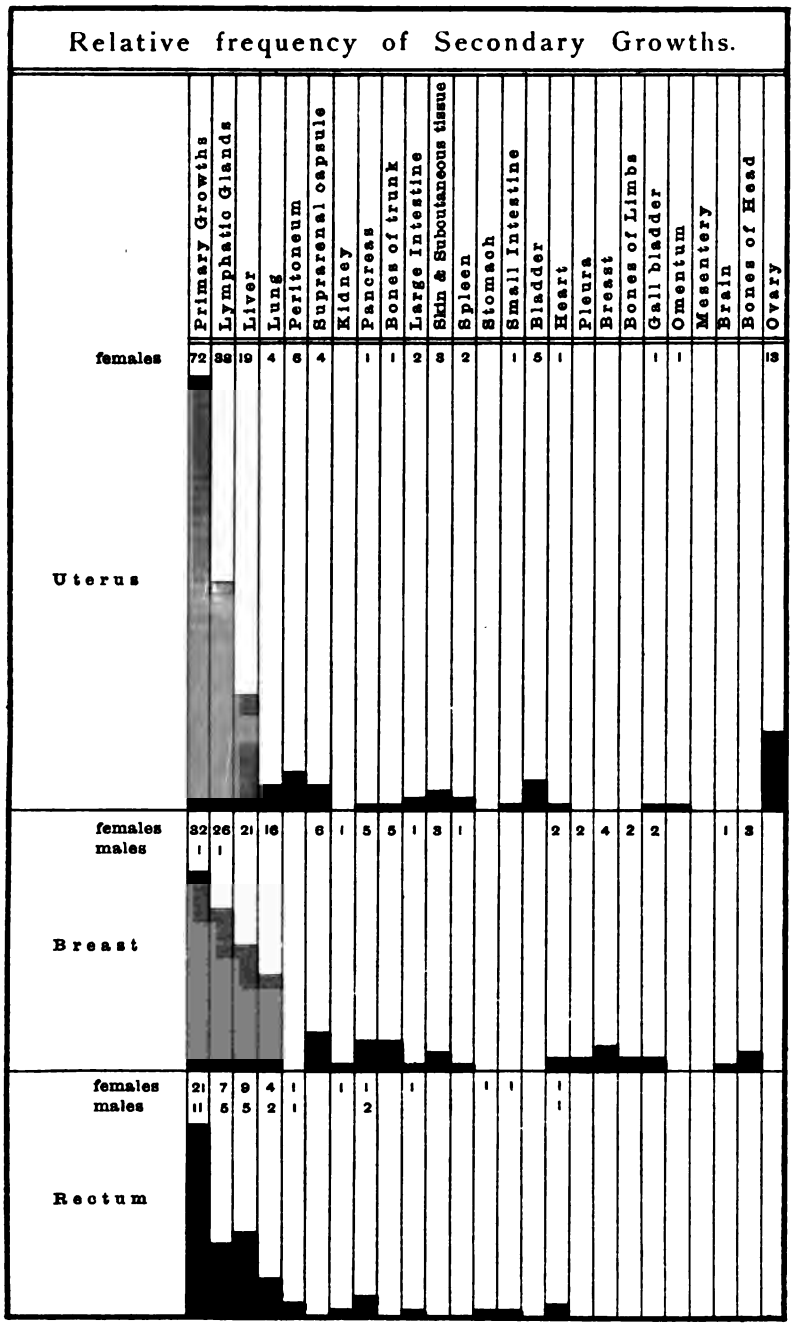
Seat of New Growth.	Total.	M.	F.	Proportion.	Percentage.
Uterus . . .	23	—	23	$\frac{23}{72}$	31·94
Rectum . . .	12	5	7	$\frac{12}{39}$	30·76
Lip	2	2	—	$\frac{2}{6}$	33·33
Palate . . .	1	1	—	$\frac{1}{3}$	33·33
Tongue . . .	9	7	2	$\frac{9}{23}$	39·13
Œsophagus . .	3	3	—	$\frac{3}{8}$	37·5
Stomach . . .	1	1	—	$\frac{1}{19}$	5·26
Liver . . .	2	1	1	$\frac{2}{4}$	50
Pancreas . . .	1	—	1	$\frac{1}{9}$	11·11
Colon . . .	3	—	3	$\frac{3}{5}$	60
Bladder . . .	4	2	2	$\frac{4}{11}$	36·36

This list is to be compared with the cases shewn on PLATES VII. and VIII., and the denominator in the fourth column gives the total number of post-mortem examinations made.

Certain parts were found to be the seat of a secondary new growth in a single case only, and are not referred to in PLATES VII. and VIII. Thus a secondary new growth was found once—in the thyroid gland in a case of carcinoma of the soft palate in a man; in the tonsil in a case of carcinoma of the lip in a man; on the cranial aponeurosis in a case of carcinoma of the breast in a woman; and in the anterior mediastinum (? arising in a lymphatic gland) in a case of carcinoma of the breast in a woman.

In the case of organs covered by a serous membrane care has been taken to distinguish as far as possible between new growth occurring on the surface of the membrane and that occurring in the substance of the organ beneath.


Site of Primary Growth.
Breast
Tongue
Rectum
Stomach
Lip
Bladder
Pancreas
Œsophagus
Colon
Larynx
Liver
Palate
Cheek mucous membrane
Skin, face and scalp
" nose
" trunk and limbs
Kidney
Bileduct
Maxilla
Parotid gland
Omentum
Bronchus
Uterus
Penis
Vulva
Prostate
Scrotum
Testicle
Skin,--Rodent ulcer
FEMALES.
131 6 25 7 6 8 6 2 1 3 2 1 1 1 2 1 78 5 8 279
MALES.
8 41 14 12 12 5 6 8 1 3 3 4 4 1 2 1 1 1 6 3 2 1 5 140


Relative frequency of Secondary Growths.
Primary Growths
Lymphatic Glands
Liver
Lung
Peritoneum
Suprarenal capsule
Kidney
Pancreas
Bones of trunk
Large Intestine
Skin & Subcutaneous tissue
Spleen
Stomach
Small Intestine
Bladder
Heart
Pleura
Breast
Bones of Limbs
Gall bladder
Omentum
Mesentery
Brain
Bones of Head
Ovary
Uterus
females 72 38 19 4 6 4 1 1 2 3 2 - 5 2 - - - - - - - 13
Breast
females 32 26 21 16 6 1 5 5 1 3 1 2 2 4 2 2 1 3
males 1 1
Rectum
females 21 7 9 4 1 1 1 1
males 11 5 5 2 1 2 1 1 1

Relative frequency of Secondary Growths.

	Primary Growths	Lymphatic Glands	Liver	Lung	Peritoneum	Suprarenal capsule	Kidney	Pancreas	Bones of trunk	Large Intestine	Skin & Subcutaneous tissue	Spleen	Stomach	Small Intestine	Bladder	Heart	Pleura	Breast	Bones of Limbs	Gall bladder	Omentum	Mesentery	Brain	Bones of Head	Ovary
Lip males	6	3	1	1																					
Palate males	3	2																							
Tongue females	3	1																							
Tongue males	20	12	1	2			1																		
Œsophagus males	3	4	1	2			2		1				1				1		1						
Stomach females	7	4	1	2	2					2												2			
Stomach males	12	6	7		2	2		1					1										1		
Liver females	1																								
Liver males	3	2	1	1																					
Pancreas females	3	2	2	1	1		1					1									1				1
Pancreas males	6	2	5		1					1							1								
Colon females	4	1	1																						
Colon males	1		1																						
Bladder females	6	3				1																			
Bladder males	3	1																							

DESCRIPTION OF PLATES VI., VII., AND VIII.

PLATE VI.

Diagram shewing the seat of primary growth in 249 cases of carcinoma.

PLATES VII. AND VIII.

Diagrams shewing the relative frequency with which various parts and organs shewed secondary new growths in 223 cases of carcinoma.

THE BACTERIOLOGICAL EXAMINATION OF CASES OF CARCINOMA AND SARCOMA.

By ALEXANDER G. R. FOULERTON, F.R.C.S., and CECIL PRICE-JONES, M.B.

Amongst the various theories which attribute the causation of carcinoma to the action of some vegetable or animal parasite, there is none that has obtained wider credence than the one first enunciated in 1890 by Russell of Edinburgh, and afterwards elaborated by San Felice, Roncali, and others, which assumes that certain species of blastomycetes are the causative agents. In a recent Paper by one of us* the various prevalent theories with regard to the alleged parasitic causation of carcinoma and sarcoma were discussed, and conclusions in the sense following were arrived at:—

(1.) That carcinoma has not the general characters of an infective disease caused by a parasite from without.

(2.) That, with regard to the theories as to a protozoal causation, the evidence which has been brought forward to prove the presence of sundry specific "parasites" is insufficient to establish the exact nature of the bodies described; and that, granting that the alleged "parasites" might be protozoa, evidence to connect them with the disease in casual relationship is wanting.

(3.) That similar objections apply to the theories which assume a vegetable parasite as the causative agent; and that with regard to the blastomycetic theory of the causation of carcinoma, in particular, much of the evidence which has been brought forward by the upholders of it is untrustworthy.

* Foulerton, "The Causation of Carcinoma and Sarcoma." ("The Practitioner," July and August, 1902.)

(4.) That, whilst carcinoma has not the general characters of an infective parasitic disease, it is quite possible that some of the cases which clinically, at any rate, are included amongst the sarcomata may prove to come within that category.

We may briefly recapitulate the character of the evidence which has been brought forward in support of the blastomycetic theory in particular. Such evidence may be described under three heads: the morphological evidence afforded by the supposed resemblance between the "cancer bodies" seen in the epithelial cells of a carcinoma, and the yeast cells which may be seen in the granulomata produced in the infection of experimental animals with pathogenic yeasts; the biological evidence afforded by the alleged "isolation" of yeasts from cases of carcinoma; and the experimental evidence afforded by the alleged production of adeno-carcinoma by Sanfelice, and of lesions described by other writers as "endotheliomata," "malignant epithelial new growth," "malignant tumours of endothelial origin," and the like, by inoculation with so-called "cancer yeasts."

The evidence founded on morphological appearances, and the alleged results obtained by the inoculation of experimental animals with "cancer yeasts," were discussed in detail in the Paper referred to; and the evidence so far was considered to be either in some cases insufficient, or in other cases absolutely untrustworthy. With regard to the biological evidence afforded by the alleged isolation of yeasts from malignant tumours, reasons were given for doubting the significance attached to their results by writers who claim, in one or two cases, to have obtained such cultures; it seemed obvious that such results might have been merely accidental.

And amongst the bacteriological evidence quoted as against the probability of carcinoma being due to a blastomycetic causation, was that of Malvoz and Brouha, who found that whereas the serum of experimental animals that had been inoculated with "cancer," and other, yeasts developed a certain degree of agglutinative reaction, more or less specific for the species of blastomyces with which the inoculation had been made, the serum of patients with carcinoma did not give any agglutinative reaction with cultures of "cancer yeasts."

In addition to a long series of attempts to obtain cultures of organisms from cases of carcinoma and sarcoma, which had previously been made by one of us, a series of fifty-six cases have recently been examined bacteriologically, and more especially in order to control the results of those who claim to have isolated pathogenic yeasts from cases of carcinoma. Excluding cases 33 and 55, the remaining fifty-four were amongst the first five hundred cases of malignant disease investigated in the Cancer Research Laboratories. These fifty-four cases, or rather more than 10 per cent. of the whole series, were not selected with any special care, except that in the majority of the cases no ulceration of the new growth had occurred, and that in many of these cases there was perhaps unusually rapid growth, or a particularly wide dissemination of the disease; features which some might think were especially suggestive of parasitic causation. This reason accounts for the presence on the list of a certain number of cases in which the examination was made after death, cases which in a general way are less suitable for bacteriological examination than operation cases, because of the frequency of casual terminal infections in malignant disease.

The examination of all cases was carried out in the same way. If the tumour was removed by operation it was brought into the laboratory and examined as soon as possible, in most cases at once; in a few cases, noted in the table, an interval of a few hours elapsed. The culture tubes were inoculated in the following way: A cut was made into the substance of the tumour, the exposed surface was seared, and a stout platinum wire with a broad spear-shaped head was thrust into the substance of the tumour, and rotated so as to pulp up the new growth. On withdrawing the wire a certain amount of pulped-up growth was brought away on the head, and this was spread out on the surface of a culture tube.

The number of tubes inoculated from each case, and some general details, are given in the table at the end of this. The culture media used were: nutrient gelatin, nutrient agar, maltose agar, glycerin agar, horse serum, and broth. The tubes were as a rule kept in the incubator for a period of six weeks. In the majority of the cases the media used were prepared with an infusion of human muscle, obtained from cases of amputa-

tion and the like, instead of with ordinary pepton beef broth. The human muscle broth was prepared by the ordinary method in use for pepton beef broth.

This human muscle broth seemed preferable to the infusion of carcinomatous tumours which has been recommended for the growth of "cancer yeasts." If carcinoma were really due to a parasite, one would not by preference select the tissues of a person suffering from a more or less chronic infection as the most favourable medium for the growth of the parasite under artificial conditions.

Some of the culture tubes were incubated under ærobic and others under anærobic conditions, preference being given to the former. It has been said that at any rate one "cancer yeast" grows better under anærobic than under ærobic conditions, but it appears to us that if there were a specific organism for carcinoma it would be essentially an ærobic one, for we are not aware of any preferentially anærobic parasite which is capable of producing the widely disseminated lesions which may develop in the course of a case of carcinoma.

The results of our attempts at obtaining cultures in this series may be summarized as follows:—

Fifty-six cases were examined, thirty-seven cases of carcinoma and nineteen of sarcoma. With thirty cases of carcinoma in which tumours were removed by operation during life, in only ten of the cases did every tube of the series inoculated remain sterile throughout the incubation; bacterial growth was obtained on one or more tubes of the series in each of the other twenty cases. In these twenty cases we judged that in at least nine there was no room for doubt but that the growth resulted from aerial contamination; and in some of the other eleven cases also the same cause almost certainly came into play. In others of these eleven the surface of the growth was ulcerated, and its substance had become invaded by bacteria. In seven cases of carcinoma the bacteriological examination of the new growth was made after death; in one case the whole series of tubes inoculated remained sterile, in the other six growth occurred on several tubes. In two out of these six cases the growth appeared to be due to the growth of bacteria in the tissues after death; in the other four the presence of bacteria was probably associated with a terminal infection.

Nineteen cases of sarcoma were examined, a series of tubes being inoculated in sixteen cases from tumours removed by operation during life; in the remaining three cases the examination was made after death. Of the sixteen cases in which examination was made after operation, the series of tubes inoculated remained sterile in twelve; and in the remaining four, in which bacterial growth occurred, such growth appeared to us to be due to aerial contamination in at least three cases, and possibly so in the fourth. In three cases of sarcoma examined after death bacterial growth, which was in all cases probably accidental, was obtained.

We do not pretend that our rough classification of the source of bacterial growth, whether from aerial contamination, from terminal infection, or from invasion of the tissues by bacteria after death, is an accurate one; we only give the impression formed from the results of examination of the culture-tubes, taken in consideration with the circumstances under which the inoculation of the tubes was carried out.

The essential points for our present purpose are: that in rather more than ten per cent. of a series of five hundred cases of malignant disease, cultivation of organisms from the new growth by bacterial methods was attempted; that in no case was a culture of a yeast obtained, even as an obvious accidental contamination; and that in a considerable proportion of the cases bacterial growth of one sort or another did occur, such growth being apparently, in all cases, the result of more or less accidental causes.

The conclusions which we have drawn from this short series of experiments, and from the results of previous experiments in the same direction, are:—

(1.) That in making attempts at obtaining cultures from malignant growths, there are at least three possible sources of fallacy to be taken into consideration before any conclusions can be drawn from the appearance of growing organisms on the culture-tubes inoculated.

In the first place, under the conditions of such attempted cultivations, contamination of aerial origin is liable to occur in a certain proportion of the cases. And the probability of such aerial contamination is in this kind of work rather greater than in the ordinary run of bacteriological work, because of the

comparatively long procedure necessary when inoculating the culture-tubes.

And procedures which involve the cutting out of pieces of the new growth for implantation on the culture media are attended by a still stronger probability of aerial contamination than was manifested in the use of the particular procedure which we adopted in this series.

And whilst in this series of fifty-six cases it so happened that no culture of a yeast was obtained as the result of such aerial contamination, it is certain that sooner or later, had the series been prolonged, such a culture would have occurred from this cause.

And therefore the occasional growth of a yeast, such as some writers have recorded, occurring in one or two out of a long series of experiments, has not necessarily any significance whatever when considering the causation of carcinoma. Before the presence of such yeasts can be held to be of any significance in relation to the causation of the disease, it must be shewn that such yeasts have not been due to aerial contamination. And incidentally it may be added that yeasts such as are liable to occur on culture-tubes, as the result of accidental aerial contamination, have been proved to be capable of producing, when inoculated into animals, precisely the same effect as has been obtained with the alleged "cancer yeasts"—the formation of granulomata.

Two other sources of fallacy have also to be taken into account, that bacteria may be obtained from new growths as the result of terminal infection, and also as the result of casual invasion of bacteria when the surface of the growth is ulcerated; and possibly also from the accidental presence of bacteria in the substance of tumours even when the surface is not ulcerated, and apart from the occurrence of what are known as terminal infections. Our reason for believing that bacteria may occasionally be found in malignant new growths under the last-mentioned circumstances is the fact that we have occasionally obtained from tumours removed by operation, and examined bacteriologically immediately afterwards, cultures of bacteria which apparently were not of a saprophytic nature on a considerable proportion, or on all, of a series of culture-tubes inoculated.

With regard to these possible sources of fallacy, we do not consider that the presence of yeasts in cultures obtained from malignant new growths is very likely to occur from any except the first, that is to say, from aerial contamination.

(2.) The other conclusion at which we have arrived is, that the results, both of our own experiments and of those made by others, shew the improbability of any of the "cancer yeasts," which have hitherto been described as the cause of carcinoma, having any causal relationship whatever with the disease.

Such described "cancer yeasts" apparently grow readily on ordinary bacteriological culture media, and, if they were constantly present in cases of malignant disease, as they must necessarily be if they are cause of it, one would certainly find that they were obtainable in culture in a larger proportion of cases than could reasonably be explained by assuming that they were the result of aerial contamination.

TABLE OF CASES OF CARCINOMA AND SARCOMA FROM WHICH CULTIVATIONS WERE ATTEMPTED.

	Sex, Age, and Number in Cancer Register.	Site and nature of primary new growth.	Number of tubes inoculated.		
			For ærobic culture.	For anærobic culture.	
1	F., 36 years. 148, 1900.	Spheroidal-celled carcinoma of breast. (l.)	4	4	Operation case. No growth obtained.
2	F., 39 years. 143, 1900.	„ „ „ (r.)	4	2	Operation case. No growth obtained.
3	F., 45 years. 326, 1901.	„ „ „ (r.)	10	—	Operation case. Axillary glands affected. Tubes inoculated from growth in breast. Four tubes shewed bacterial growth at end of four weeks.
4	F., 46 years. 274, 1901.	„ „ „ (l.)	9	3	Operation case. One tube shewed growth of saprophytic bacillus at end of six weeks.
5	F., 47 years. 221, 1900.	„ „ „ (r.)	9	3	Bacteriological examination made twenty-two hours after death. Tubes inoculated from affected cervical glands. All tubes shew growth of various organisms—*B. subtilis*, cocci, and moulds.
6	F., 48 years. 332, 1901.	„ „ „ (r.)	10	—	Operation case. No growth obtained.
7	F., 49 years. 141, 1900.	„ „ „ (r.)	6	2	Operation case. Bacterial growth on five of ærobic tubes, remainder sterile.
8	F., 49 years. 276, 1901.	„ „ „ (l.)	9	3	Operation case. Three tubes shew growth of *B. subtilis* and a mould, remainder sterile.

	Sex, Age, and Number in Cancer Register.	Site and nature of primary new growth.	Number of tubes inoculated. For aerobic culture.	Number of tubes inoculated. For anaerobic culture.	
9	F., 51 years 107, 1900.	Spheroidal-celled carcinoma of breast. (r.)	12	3	Operation case. Axillary glands affected. Culture tubes inoculated from new growth in breast. Most of the tubes shew the growth of a coccus in white colonies, probably *S. pyogenes albus*.
10	F., 53 years. 103, 1900.	„ „ „ (l.)	4	2	Operation case. Axillary glands affected. Culture tubes inoculated from new growth in breast. Several tubes shew growth of a coccus resembling that in case 9.
11	F., 53 years. 132, 1900.	„ „ „ (l.)	5	3	Operation case. No growth obtained.
12	F., 54 years. 35, 1900.	„ „ „ (l.)	10	4	Operation case. No growth obtained.
13	F., 56 years. 86, 1900.	„ „ „ (r.)	10	3	Operation case. No growth obtained.
14	F., 56 years. 207, 1900.	„ „ „ (r.)	9	3	Operation case. No growth obtained.
15	F., 57 years. 211, 1900.	„ „ „ (r.)	9	3	Operation case. All tubes shew growth of a coccus, liquefying gelatin after about ten days' incubation at 22° C.; not stained by Gram's method.
16	F., 57 years. 112, 1900.	„ „ „ (l.)	7	4	Operation case. Axillary glands removed. Tubes inoculated from the new growth in breast. Growth of (?) saprophytic bacillus on most of the tubes inoculated.

	Sex, Age, and Number in Cancer Register.	Site and nature of primary new growth.	Number of tubes inoculated.		
			For ærobic culture.	For anærobic culture.	
17	F., 58 years. 298, 1901.	Spheroidal-celled carcinoma of breast. (r.)	6	—	Both breasts, cervical and axillary glands affected. Bacteriological examination made some hours after death. Cultures made from growth in breast and also from blood in heart. All tubes shew a pure culture of *B. pyocyaneus*.
18	F., 60 years. 37, 1900.	„ „ „ (l.)	12	6	Operation case. Two of the anærobic tubes shewed growth of a sporing saprophytic bacillus.
19	F., 60 years. 84, 1900.	„ „ „ (l.)	6	3	Operation case. No growth obtained.
20	F., 60 years. 275, 1901.	„ „ „ (l.)	9	3	Operation case. No growth obtained, except mould on two tubes after six weeks.
21	F., 61 years. 116, 1900.	„ „ „ (l.)	4	4	Operation case. Growth of (?) saprophytic bacillus on two tubes.
22	F., 62 years. 222, 1900.	„ „ „ (r.)	9	3	Operation case. Growth of cocci on several of the tubes inoculated.
23	F., 63 years. 239, 1900.	„ „ „ (r.)	9	3	Operation case. Growth of cocci on three tubes, remainder sterile.
24	F., 47 years. 79, 1900.	Columnar-celled carcinoma of breast. (r.)	6	3	Operation case. Tubes inoculated several hours after removal of growth. Growth of cocci on five tubes, remainder sterile.

	Sex, Age, and Number in Cancer Register.	Site and nature of primary new growth.	Number of tubes inoculated.		
			For aerobic culture.	For anaerobic culture.	
25	M., 64 years. 220, 1900.	Spheroidal-celled carcinoma of breast (r.)	9	3	Operation case. Growth of (?) saprophytic bacillus on two tubes, remainder sterile.
26	M., 49 years. 289, 1901.	Columnar-celled carcinoma of rectum.	6	—	Cultures made after death from a nodule of secondary growth in the liver which was breaking down; pure culture of *S. pyogenes aureus* on every tube.
27	F., 59 years. 297, 1901.	„ „ „	6	—	Cultures made after death from a secondary nodule in the liver and from the heart's blood. No growth obtained.
28	M., 67 years. 237, 1901.	„ „ „	9	3	Operation case. Bacterial growth obtained on all tubes, *B. coli communis*, and a coccus.
29	F., 44 years. 266, 1901.	Squamous-celled carcinoma of cervix of uterus.	6	2	The cultures were inoculated after death from a mass of new growth which occupied the position of the cervix uteri, and was extensively ulcerated on its surface. A free growth of bacilli was obtained on all the tubes.
30	F., 54 years. 213, 1900.	„ „ „	3	—	Tubes were inoculated from peritoneal fluid removed during life by paracentesis abdominis. No growth obtained.
31	F., 54 years. 238, 1900.	„ „ „	9	3	Culture tubes inoculated from the new growth four and a half hours after death. Five tubes shewed cultures of *B. pyocyaneus*, the others various bacterial growth.

	Sex, Age, and Number in Cancer Register.	Site and nature of primary new growth.	Number of tubes inoculated.		
			For ærobic culture.	For anærobic culture.	
32	F., 20 years. 119, 1900.	Spheroidal-celled carcinoma of pylorus.	12	5	Culture tubes inoculated from thoracic glands eight hours after death. All tubes shew bacterial growth.
33	M., 54 years. Surgical Register 1591, 1899.	Squamous-celled carcinoma of penis.	6	3	Operation case. No growth obtained.
34	M., 68 years. 219, 1900.	Squamous-celled carcinoma of lip.	4	—	Operation case. Growth of *S. pyogenes aureus* on two tubes, others sterile.
35	M., 59 years. 198, 1900.	Squamous-celled carcinoma of tongue.	9	3	Operation case. All tubes shew growth of staphylococci and streptococci.
36	M., 59 years. 248, 1900.	„ „ „	9	3	Operation case. Growth of cocci on two tubes, remainder sterile, except for appearance of moulds on one or two later.
37	F., 58 years. 206, 1900.	Carcinoma of skin of face (rodent ulcer).	2	—	Operation case. Growth of cocci obtained on both tubes.
38	F., 42 years. 72, 1900.	Spindle-celled sarcoma of breast. (r.)	6	2	Operation case. No growth obtained.
39	F., 44 years. 202, 1900.	Round-celled sarcoma of breast. (r.)	9	3	Operation case. No growth obtained.
40	F., 50 years. 329, 1901.	„ „ „ (l.)	10	—	Operation case. Axillary glands affected. Culture tubes inoculated from growth in breast. Saprophytic contamination on three tubes, remainder sterile.

	Sex, Age, and Number in Cancer Register.	Site and nature of primary new growth.	Number of tubes inoculated.		
			For ærobic culture.	For anærobic culture.	
41	F., 51 years. 117, 1900.	Round-celled sarcoma of breast. (r.)	4	4	Operation case. One tube shewed growth of a saprophytic bacillus.
42	F., 62 years. 165, 1900.	„ „ „ (l.)	6	2	Operation case. Axillary glands affected. Culture tubes inoculated from new growth in breast. Three colonies of cocci on one tube, remainder sterile.
43	F., 59 years. 106, 1900.	Hæmangio-sarcoma of breast. (l.)	6	3	Operation case. Axillary glands affected. Growth of sarcinæ on two tubes, remainder sterile.
44	M., 19 years. 133, 1900.	Round-celled sarcoma growing from os ilium. (r.)	3	3	Bacteriological examination made twenty-four hours after death. Free bacillary growth on all tubes.
45	F., 14 years. 15, 1900.	Round-celled sarcoma growing from femur. (l.)	10 9	2 3	Operation case. The first bacteriological examination was made when the thigh was amputated; the second one eleven hours after the death of the patient with recurrence of the disease in the inguinal region. At first examination made during life all the tubes inoculated remained sterile; at the examination made after death a bacillary growth was obtained on all the tubes.
46	M., 19 years. 8, 1900.	„ „ „ (r.)	7	4	Operation case. No growth obtained.
47	M., 23 years. 264, 1901.	Myeloid sarcoma growing from tibia. (l.)	9	3	Operation case. No growth obtained.

	Sex, Age, and Number in Cancer Register.	Site and nature of primary new growth.	Number of tubes inoculated.		
			For aerobic culture.	For anaerobic culture.	
48	M., 63 years. 110, 1900.	Round-celled sarcoma growing from mandible.	7	4	Operation case. No growth obtained.
49	F., 70 years. 210, 1900.	Lympho-sarcoma growing in neck.	9	3	Bacteriological examination carried out several hours after death; culture tubes inoculated from cervical growth and from a nodule in the liver; bacillary growth obtained on all tubes.
50	M., 60 years. 330, 1901.	Round-celled sarcoma growing in subcutaneous tissue of fore-arm. (r.)	9	—	Operation case. No growth obtained.
51	F., 35 years. 97, 1900.	Round-celled sarcoma growing in subcutaneous tissue of neck.	5	3	Bacteriological examination made two hours after death; culture tubes inoculated from nodule of new growth in the liver. Moulds appeared on three tubes, remainder sterile.
52	F., 26 years. 243, 1900.	Round-celled sarcoma growing in ischio-rectal fossa.	9	3	Operation case. No growth obtained.
53	F., 56 years. 270, 1901.	Round-celled sarcoma growing near anus.	9	2	Operation case. Culture tubes were inoculated from a small nodule removed from the subcutaneous tissue over the abdomen, where there had been recurrence of the disease after removal of the primary tumour. No growth obtained.
54	M., 58 years. 17, 1900.	Round-celled sarcoma growing in subcutaneous tissue of thigh. (l.)	11	3	Operation case. No growth obtained.

	Sex, Age, and Number in Cancer Register.	Site and nature of primary new growth.	Number of tubes inoculated.		
			For aerobic culture.	For anaerobic culture.	
55	F., 40 years. Surgical Register 1421, 1899.	Melanotic round-celled sarcoma growing in subcutaneous tissue of leg.	3	3	Operation case. No growth obtained.
56	F., 68 years. 11, 1900.	Melanotic round-celled sarcoma growing in labium minus.	8	4	Operation case. Culture tubes inoculated from primary growth, and from affected inguinal glands removed at the same time. No growth obtained.

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